ASSOCIATION OF GAMMA GLUTAMYL TRANSFERASE

WITH ACUTE CORONARY SYNDROME AND

CORRELATION WITH IN-HOSPITAL OUTCOME

Dissertation submitted to

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In partial fulfillment of regulations

For award of the degree of

M.D (GENERAL MEDICINE)

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BONAFIDE CERTIFICATE

This is to certify that dissertation named **"ASSOCIATION OF GAMMA GLUTAMYL TRANSFERASE WITH ACUTE CORONARY SYNDROME AND CORRELATION WITH IN-HOSPITAL OUTCOMES"** is a bonafide work performed by Dr.Rizwan Ahamed Z, post graduate student, Department of Internal Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in fulfillment of regulations of the Tamilnadu Dr. M.G.R Medical University for the award of M.D. Degree Branch I (General Medicine) during the academic period from May 2011to April 2014.

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DECLARATION

I solemnly declare that this dissertation **"ASSOCIATION OF GAMMA GLUTAMYL TRANSFERASE WITH ACUTE CORONARY SYNDROME AND CORRELATION WITH IN-HOSPITAL OUTCOME"** was prepared by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of **Dr.R.Sabaratnavel M.D.**, Professor, Department of Internal Medicine, Government Royapettah Hospital, Chennai.

This dissertation is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the University regulations for the award of the degree of **M.D. Branch I (General Medicine)**.

Place: Chennai

Date: (Dr. RIZWAN AHAMED Z)

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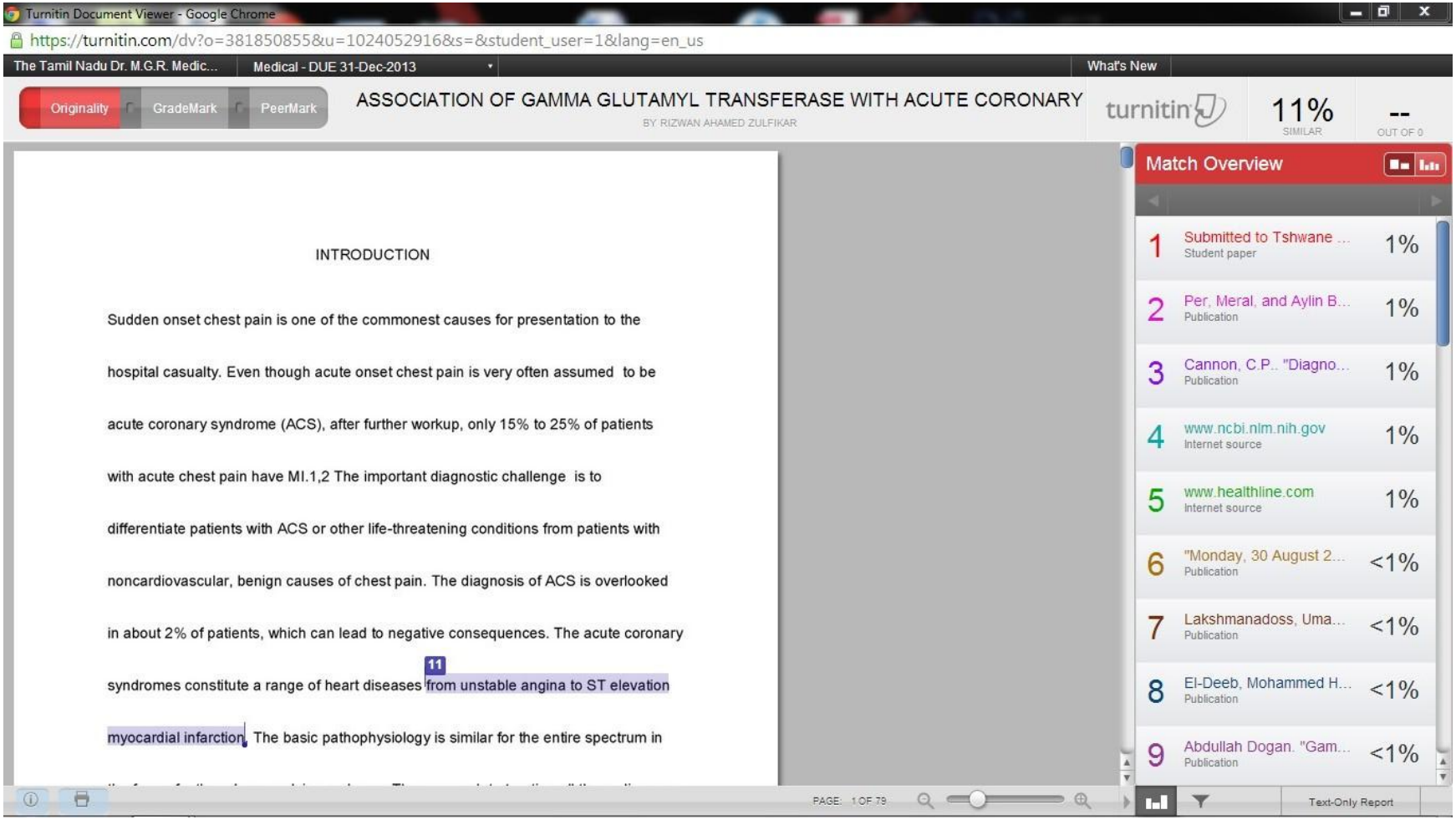
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INTRODUCTION
Sudden onset chest pain is one of the commonest causes for presentation to the hospital casualty. Even though acute onset chest pain is very often assumed to be acute coronary syndrome (ACS), after further workup, only 15% to 25% of patients with acute chest pain have MI.1,2 The important diagnostic challenge is to differentiate patients with ACS or other life-threatening conditions from patients with noncardiovascular, benign causes of chest pain. The diagnosis of ACS is overlooked in about 2% of patients, which can lead to negative consequences. The acute coronary syndromes constitute a range of heart diseases from unstable angina to ST elevation myocardial infarction. The basic pathophysiology is similar for the entire spectrum in
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INTRODUCTION Sudden onset chest pain is one of the commonest causes for presentation to the hospital casualty. Even though acute onset chest pain is very often assumed to be acute coronary syndrome (ACS), after further workup, only 15% to 25% of patients with acute chest pain have MI.1,2 The important diagnostic challenge is to differentiate patients with ACS or other life-threatening conditions from patients with noncardiovascular, benign causes of chest pain. The diagnosis of ACS is overlooked in about 2% of patients, which can lead to negative consequences. The acute coronary syndromes constitute a range of heart diseases

from unstable angina to ST elevation myocardial infarction. 11

The basic pathophysiology is similar for the entire spectrum in the form of a thrombus overlying a plaque. The approach to treating all these diseases is fundamentally similar but with certain unique features depending on the type of acute coronary syndrome. Several recent advances have enhanced the accuracy and effi¬ciency of the evaluation of patients with acute chest pain, mainly owing to better biomarkers of cardiac injury3. Cardiac markers are proteins released into the circulation when cardiac cells die. These are troponin I, troponin T, myoglobin and CK-MB . These cardiac markers play an essential role in diagnosing as well as stratifying acute coronary syndrome (ACS). A variety of molecules have been used to diagnose and prognosticate acute coronary syndromes ranging from LDH and myoglobin to creatine phosphokinase and troponins. The current management particulars are centered around the measurements of troponins which are both highly specific and sensitivity to acute cardiac insult. However the search is still ongoing for other molecules and enzymes which will help in assessing the severity of various forms of myocardial infarction. Stratification of ACS into high and low risk is imperative not only regarding the adequacy of treatment but can also in avoiding unnecessary costs and inconvenience to the patient. Among the latest armamentarium of molecules being investigated for diagnosing and more importantly, prognosticating myocardial infarction is an enzyme called Gamma Glutamyl Transferase(GGT).4 Well recognised as a marker of alcohol induced liver injury, GGT has gained importance in recent years as a marker of acute cardiac injury and has shown correlation with a host of risk factors responsible for macrovascular diseases, primarily coronary artery disease. GGT shows promise as a new tool in the risk stratification of various types of acute myocardial infarction. AIMS AND OBJECTIVES OF THE STUDY 1. To determine the frequency of raised serum Gamma Glutamyl Transferase levels in cases presenting with acute coronary syndromes. 2. To determine the possible association between raised GGT levels and different subsets of ACS. 3. To determine the

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CONTENTS

ASSOCIATION OF GAMMA GLUTAMYL TRANSFERASE LEVELS WITH ACUTE CORONARY SYNDROME AND CORRELATION WITH IN-HOSPITAL OUTCOME

ABSTRACT

BACKGROUND: Although traditionally associated with alcoholic liver disease, recent studies have shown evidence of correlation between elevated Gamma-glutamyltransferase (GGT) and atherosclerotic heart disease. This is said to be due to its role in the generation of reactive oxygen species in the presence of iron. It is independently correlated with conditions associated with increased atherosclerosis, such as obesity, elevated serum cholesterol, high blood pressure and myocardial infarction. It is also demonstrated that serum GGT activity is an independent risk factor for myocardial infarction and cardiac death in patients with coronary artery disease.

AIM: To study the correlation between rise in GGT levels and different subsets of Acute Coronary Syndrome. To study the correlation between GGT and risk of Major Adverse Cardiovascular Events(MACE).

MATERIALS AND METHODS: This is a cross sectional study conducted at Government Royapettah Hospital and patients admitted with Acute Coronary Syndrome in our ICU were selected. GGT levels were measured for all patients

in a standardized manner and cases were observed for five days in the hospital for adverse events. This study was done for a time period between May 2013 to October 2013 and 75 patients with ACS were included.

RESULTS AND OBSERVATIONS: Serum GGT levels were significantly elevated in both the STEMI and NSTEMI subsets but not in the unstable angina subset. The mean GGT value for patients who suffered complications is 90.22. The mean value for patients without MACE is a significantly less 46.44. There was also found to be correlation between GGT and presence of hypertension, LV dysfunction, total cholesterol and LDL levels.

CONCLUSION: Gamma glutamyltransferase levels were significantly elevated above normal in patients presenting with acute coronary syndrome. GGT levels were independently correlated with STEMI and NSTEMI but had no correlation with unstable angina. There was a significant correlation between GGT levels and incidence of left ventricular systolic LV dysfunction. The mean value of GGT was significantly elevated in patients who suffered from major adverse cardiovascular events. Patients with significantly elevated GGT values may, in future, be referred for early invasive revascularization procedures like PCI/CABG. In conclusion, as concerns ischemic heart disease, GGT assay seems to have the features of a good prognostic marker with optimal sensitivity of the diagnostic assay and it helps improve our ability to predict adverse events

in CAD. Further its prognostic impact can be utilized in risk stratification and the need for urgent therapeutic intervention.

KEYWORDS: Gamma Glutamyl Transferase, Acute Coronary Syndrome, LDL oxidation, atherosclerotic plaque, MACE.

INTRODUCTION

Sudden onset chest pain is one of the commonest causes for presentation to the hospital casualty. Even though acute onset chest pain is very often assumed to be acute coronary syndrome (ACS), after further workup only 15% to 25% of patients with acute chest pain have MI.[1,2] The important diagnostic challenge is to differentiate patients with ACS or other life-threatening conditions from patients with noncardiovascular, benign causes of chest pain. The diagnosis of ACS is overlooked in about 2% of patients, which can lead to negative consequences. The acute coronary syndromes constitute a range of heart diseases from unstable angina to ST elevation myocardial infarction. The basic pathophysiology is similar for the entire spectrum in the form of a thrombus overlying a plaque. The approach to treating all these diseases is fundamentally similar but with certain unique features depending on the type of acute coronary syndrome. Several recent advances, have enhanced the accuracy and efficiency of the evaluation of patients with acute chest pain, mainly owing to better biomarkers of cardiac injury.[3]

Cardiac markers are proteins released into the circulation when cardiac cells die. These are troponin I, troponin T, myoglobin and CK-MB . These cardiac markers play an essential role in diagnosing as well as stratifying acute coronary syndrome (ACS). A variety of molecules have been used to diagnose

and prognosticate acute coronary syndromes ranging from LDH and myoglobin to creatine phosphokinase and troponins. The current management particulars are centered around the measurements of troponins which are both highly specific and sensitivity to acute cardiac insult. However the search is still ongoing for other molecules and enzymes which will help in assessing the severity of various forms of myocardial infarction. Stratification of ACS into high and low risk is imperative not only regarding the adequacy of treatment but also in avoiding unnecessary costs and inconvenience to the patient.

Among the latest armamentarium of molecules being investigated for diagnosing and more importantly, prognosticating myocardial infarction is an enzyme called Gamma Glutamyl Transferase (GGT).[4] Well recognised as a marker of alcohol induced liver injury, GGT has gained importance in recent years as a marker of acute cardiac injury and has shown correlation with a host of risk factors responsible for macrovascular diseases, primarily coronary artery disease. GGT shows promise as a new tool in the risk stratification of various types of acute myocardial infarction.

REVIEW OF LITERATURE

HISTORY OF MYOCARDIAL INFARCTION

Even though modern sedentary life style is unanimously blamed for the increasing prevalence of coronary artery disease, the latter seems to be as old as human civilization itself. In 2009, researchers discovered evidence of atherosclerosis and narrowed arteries in Egyptian mummies four millennia old. It was attributed to their princely lifestyle, diet rich in fat. It is known that Leonardo Da Vinci, that pioneer of all sciences, investigated diseased coronary arteries in vagabonds, a full century before William Harvey even discovered cardiac circulation. Later, Friedrich Hoffmann (1660–1742), Cardiology head at the Halle University, astutely commented that coronary heart disease started in the "reduced passage of the blood within the coronary arteries." Angina was a source of confusion to clinicians for the last two centuries. When first elaborated in 1768, it was suspected by clinicians of that day to have something to do with blood flow in the coronary arteries.

William Osler (1849–1919) studied angina extensively, and was the earliest to call it a syndrome rather than a disease. James B. Herrick (1861–1954), an American cardiologist suggested that an indolent process of occlusion of the arteries in the heart could be the reason for angina. The 1900s mark a start of a period of increasing research in coronary artery disease. A group of doctors

started the first “Association for the Prevention and Relief of Heart Disease” in New York City in 1915. Just a few years down the lane, doctors started using catheters to explore coronary arteries. The pioneers mainly responsible for this new technology were Egas Moniz (1874–1955) and physician Werner Forssman (1904–1979). This new investigation played a major role in correctly diagnosing coronary artery disease. However it was only following the initiation of the Framingham Heart Study in 1948 that the mystery behind CAD slowly started unraveling. In the 1970’s newer treatments were introduced in the form of bypass surgery and angioplasty for treating CAD. In the 1980s, stents began to be commonly used to open up narrowed arteries. The last two decades have opened up new vistas in the management of this serious disease. Therefore coronary artery disease is no longer a death sentence as a result of these latest advances in diagnosis and treatment

DEFINITION

Acute coronary syndromes are defined based on the characteristics of three cardinal elements; history of typical angina, presence or absence of changes in ECG, and markers of cardiac injury. In certain exceptional cases, a diagnosis of MI can be rarely made even in the absence of the above mentioned criteria such as in the case of a past recorded history of coronary artery disease.[5]

The pathologic diagnosis of myocardial infarction (MI) requires evidence of cardiac cell death as a result of compromised blood supply. ACS follows a

range of clinical manifestations which follow the disturbance of an atheroma and formation of an overlying thrombus. A complete block in the vessel in the absence of collateral perfusion results in ST-segment elevation (STEMI) and a non occlusive thrombus leads to non-ST-segment elevation myocardial infarction (NSTEMI). The newer definition of MI divides it into five categories depending on the scenario in which it occurs.[6]

Revised Definition of Myocardial Infarction

Criteria for Acute, Evolving, or Recent MI

Either of the following criteria satisfies the diagnosis for acute, evolving, or recent MI:

1. Typical rise and/or fall of biochemical markers of myocardial necrosis with at least one of the following:

a. Ischemic symptoms

b. Development of pathologic Q waves in the ECG

c. Electrocardiographic changes indicative of ischemia

d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

2. Pathologic findings of an acute myocardial infarction

Criteria for Healing or Healed Myocardial Infarction

Any one of the following criteria satisfies the diagnosis for healing or healed myocardial infarction:

1. Development of new pathologic Q waves in serial ECGs..

2. Pathologic findings of a healed or healing infarction

The contemporary approach to patients presenting with ischemic discomfort is to mostly assume that they are experiencing an acute coronary syndrome. The 12-lead electrocardiogram (ECG) categorizes them into ST elevation and non ST elevation MI.

The idea of acute coronary syndrome, which is based on a central pathological tenet, is invaluable in formulating treatment strategies.[7] Cases coming with ST elevation are selected for reperfusion treatment either through device or pharmacological measures. ACS patients presenting with ecg changes other than ST elevation are not selected for reperfusion therapy but should be given medical drugs for countering ischemia, followed by PCI.[8] However, antiplatelet and anticoagulant therapy is mandatory for both types. Hence, the

electrocardiogram is invaluable in the approach and treatment of cases presenting with significant chest pain. [9]

DEFINITION OF UNSTABLE ANGINA AND NON ST ELEVATION MI

"Unstable angina is defined as angina pectoris (or equivalent type of ischemic discomfort) with at least one of three characters: (1) occurring at rest (or minimal exertion) and usually lasting >20 minutes (if not interrupted by the administration of a nitrate or an analgesic); (2) being severe and usually described as frank pain; or (3) occurring with a crescendo pattern (i.e., pain that awakens the patient from sleep or that is usually more severe than previously)".[10] Around two thirds of patients with unstable angina have evidence of myocardial cell death on the basis of elevated cardiac serum markers, such as cardiac-specific troponin T or I and creatine kinase isoenzyme (CK)–MB, and thus have a diagnosis of NSTEMI.

A clinical classification of UA/NSTEMI [11] provides a useful means to stratify risk. Patients fall into three groups according to the clinical circumstances of the acute ischemic episode:

(1) *Primary unstable angina* caused by reductions in myocardial blood flow;

(2) *Secondary unstable angina* (as a result of increased demand, as in anemia); and

(3) *Post-MI unstable angina*.

CLASS	DEFINITION	DEATH OR MI TO ONE YEAR* (%)
Severity		
Class I	New onset of severe angina or accelerated angina; no rest pain	7.3
Class II	Angina at rest within past month but not within preceding 48 hr (angina at rest, subacute)	10.3
Class III	Angina at rest within 48 hr (angina at rest)	10.8†
Clinical Circumstances		
A. Secondary angina	Develops in the presence of extracardiac condition that intensifies myocardial ischemia	14.1
B. Primary angina	Develops in the absence of extracardiac condition	8.5
C. Postinfarction angina	Develops within 2 wk after acute myocardial infarction	18.5‡
Intensity of treatment	Patients with unstable angina may also be divided into three groups according to whether unstable angina occurs: (1) in the absence of treatment for chronic stable angina, (2) during treatment for chronic stable angina, or (3) despite maximal anti-ischemic drug therapy. The three groups may be designated by subscripts 1, 2, and 3, respectively.	
Electrocardiographic changes	Patients with unstable angina may be further divided into those with or without transient ST-T wave changes during pain.	

FIG-DEFINITION AND CLASSIFICATION OF UNSTABLE ANGINA

This classification provides valuable prognostic information (with postinfarction angina at rest having the worst prognosis).

EPIDEMIOLOGY

Cardiovascular disease (CVD) is accelerating fast to become one of the most important cause of mortality worldwide. In 2004, CVD caused about 30% of all deaths and 14% of all DALYs (disability adjusted life years) lost that

year.[12] The developing world is one apart of the world that is worst hit by CVD [13,14]. Increases in childhood obesity and physical inactivity are primarily responsible for the upsurge in cardiovascular mortality.[15,16] Several studies in India have suggested a rising morbidity caused by CHD in this region. Approximately 31.8 million people are living with CHD in India alone,[17] ten times more than what it was 40 years ago. Additional evidence suggests that women are more likely than men to have CVD in India.[18]

Manifestations of coronary artery disease present themselves almost a decade earlier in the Indian population compared to the west.[19] One half of the CVD deaths in India occur in people who fall below the seventh decade [20]. By 2001, CVD was responsible for 29% of all deaths and 14% of the 1.5 billion lost DALYs. [21]

Countries belonging to the south east asian region have a greater number of diabetics than in their European and American counterparts. The maximum number of diabetics are housed in China and India.[22] This can also account for the high burden of coronary artery disease and stroke in our country.

In 2006, Goyal and Yusuf[20] concluded that the prevalence of diabetes mellitus was 11.8% in urban areas and 3.8% in rural areas . Similarly, IC Health showed that prevalence was 13% in the urban setup.[23] According to the INTERHEART study, DM accounts for 11.8 of all the MI in the South East Asian region. [19]

Hypertension rates higher in its association with MI. In the Interheart study, hypertension was associated with 19.3% cases of MI.[19]

Another risk factor gaining increasing importance is overweight and obesity. Other factors that contribute to coronary artery disease have also been noted by the Interheart study. Low intake of fruits and vegetables accounts for 18.3% of MI, lack of exercise 27.1%, and lipids 58.7%. In total, a total of nine risk factors account for 89.4% of all causes of MI.[19]

PATHOLOGY OF MYOCARDIAL INFARCTION

Coronary atherosclerosis with overlying thrombus development is the cause for all MI. As the atheroma progresses, a catastrophic change occurs over the plaque resulting in the formation of a thrombus on top .[24,25] Some patients have a preexisting predilection for rupture of the plaque which is related to the oxidative status of the body.[26] Plaque rupture releases molecules that encourage the activaton of platelets which contribute to the formation of thrombus. The resultant thrombus leads to an abrupt halt in blood supply and eventual myocyte death as a result of decreased supply of oxygen.

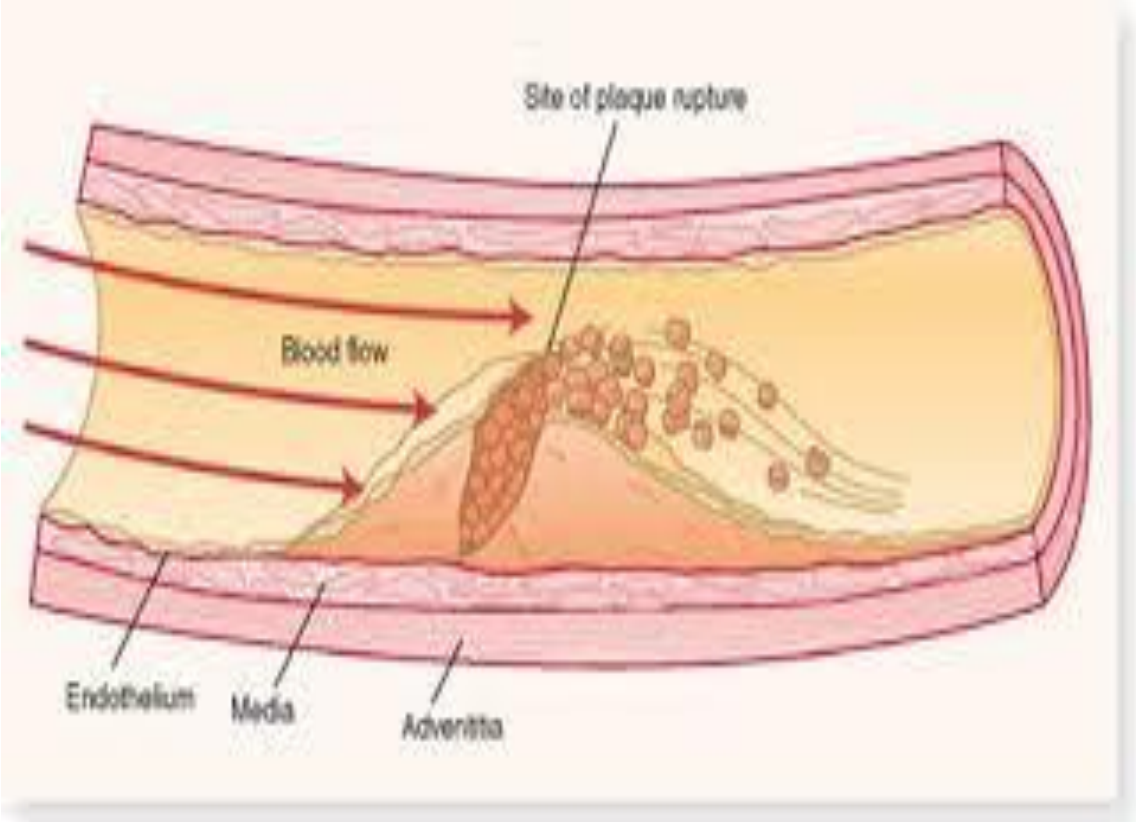


FIGURE- RUPTURE OF AN ATHEROMATOUS PLAQUE

PLAQUE FISSURING AND DISRUPTION.

Once the plaque ruptures, a variety of enzymes will be released which will breakdown the components of the atheroma.[27,28] Mast cells and macrophages which are chemotactically attracted to the plaque, release these proteinases. A variety of other factors like intraluminal pressure, vessel tone, and tachycardia act in synergy to bring about disruption. This happens at the so called 'shoulder region of the plaque', situated at the at the margin of the fibrous cap which is usually not affected by atherosclerosis.[29] Usually, completely occlusive thrombi lead to infarction of the entire thickness of the ventricular wall and usually STEMI on ecg. Cases with ECG changes other than

ST elevation are labeled as unstable angina or NSTEMI and they usually have an incomplete occlusion of the vessel; so called non occlusive thrombus.

PATHOPHYSIOLOGY OF ST ELEVATION MYOCARDIAL INFARCTION

On interruption of coronary flow, the volume of ventricular mass sustenanced by the artery shows signs of poor contraction. Four abnormal types of contraction develop in sequence:

(1) Dyssynchrony—that is, adjacent segments contracting at different times

(2) Hypokinesis-reduced contraction;

(3) Akinesis- absence of contaction and

(4) Dyskinesis- abnormal expansion and systolic bulging

If a sufficient quantity of myocardium undergoes ischemic injury, LV pump function is compromised; cardiac output and stroke volume fall[30]; and end-systolic volume rises. The degree to which end-systolic volume rises is the most important factor deciding mortality following STEMI.[31] In certain patients, a vicious circle of dilation ensues, causing further dilation. The degree of ventricular dilation depends on the size of the infarct, the amount of coronary stenosis and activation of the renin-angiotensin-aldosterone system (RAAS). It can be favorably modified by inhibitors of this system.[32]

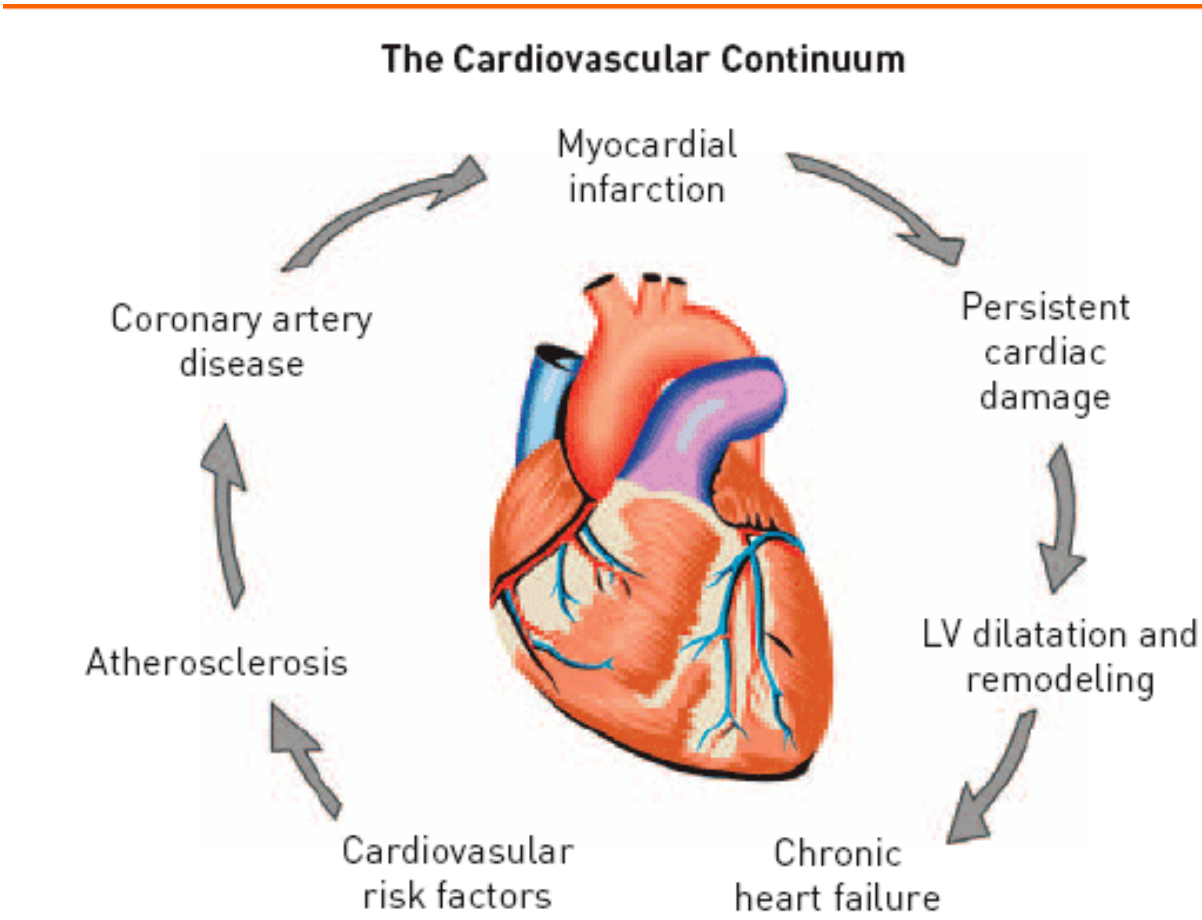


Figure- pathophysiology of myocardial infarction

If the infarcted area is more, LV function is severely depressed and the LV stroke volume falls, filling pressures rise. This leads to a marked depression of aortic pressure and decreased coronary blood flow; this condition may worsen myocardial ischemia and thereby initiate a vicious circle. Worsening LV function also leads to a rising preload. Even though this compensates to a certain level the stroke volume, the ejection fraction is compromised in the process. The dilation of the left ventricle also

increases ventricular afterload. This is because, in keeping with the Laplace's law, the ventricle will have to generate a higher wall tension in response to the grossly dilated ventricle. This increased after load increases oxygen consumption in the myocytes and worsens the ischemic process.

PATHOPHYSIOLOGY OF UNSTABLE ANGINA AND NSTEMI

The pathophysiologic processes mainly responsible for the development of UA/NSTEMI [33] are:

1. Ruptured atheromatous plaque with formation of a thrombus partially occluding it.

2. Non structural narrowing of the coronary vessels due spasm as a result of increased adrenergic activity.

3. Restenosis of coronary vessel after PCI or progressive atherosclerotic occlusion of lumen.

4. UA as a result of inflammation.

5. As a result of increased nutrition demands for instance, fever or anemia. This is labeled as secondary unstable angina.

Platelets play a major role in the conversion of a stable plaque to a devastating lesion. Break in an atherosclerotic plaque often opens up the subendothelial matrix (e.g., collagen and tissue factor) to circulating blood. The subsequent mechanisms of adhesion, activation, degranulation, and platelet aggregation leads to the formation of a thrombus.

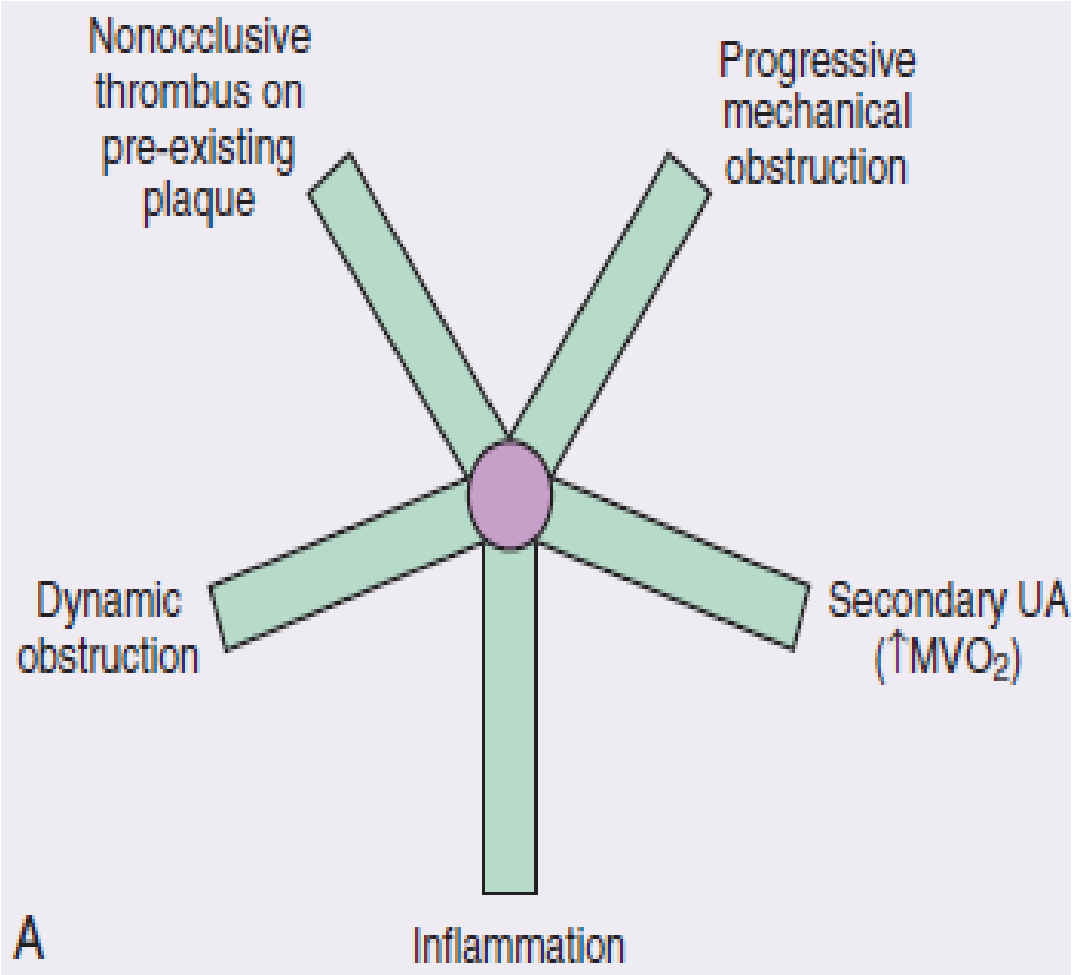


FIG-Mechanisms of unstable angina

SECONDARY HEMOSTASIS.

The coagulation system is subsequently activated as soon as the platelet plug is formed. Ultimately, the fibrin formed gets cross-linked and the clot is stabilized.

CLINICAL FEATURES OF MYOCARDIAL INFARCTION

The most crucial element in the diagnosis of ACS is the history. The prodrome is usually characterized by chest discomfort, resembling classic angina pectoris, but it occurs at rest or with less activity than usual and can therefore be classified as unstable angina. The discomfort, usually long drawn, is described as crushing or compressing and the patient usually describes the pain as if some weight is placed on his chest. The pain is classically retrosternal in location, spreading to both sides of the anterior chest, more on the left. The pain of STEMI can also radiate to the shoulders, jaw or even the teeth with some rare cases even ending up in the dental OPD. The pain can be differentiated from stable angina keeping in mind its severity and prolonged duration. Nausea and vomiting may occur, more commonly in patients with inferior STEMI .

GENERAL APPEARANCE.

Patients suffering STEMI often appear anxious and in considerable distress. They often massage or clutch their chests and frequently describe their pain with a clenched fist held against the sternum (the Levine sign).

HEART RATE.

The heart rate can vary from a marked bradycardia in cases of inferior wall involvement, to a rapid regular or irregular tachycardia, depending on the underlying rhythm and degree of LV failure.

Auscultation of the heart can be sometimes rewarding in discovering a third heart sound or rales in cases of heart failure or a new onset systolic murmur in case of a regurgitant mitral valve or a septal rupture.[34]

LABARATORY INVESTIGATIONS

ELECTROCARDIOGRAPHY

A majority of patients presenting with ACS have a host of serial electrocardiographic changes. Observation of the different leads involved can also give a clue as to which artery is involved.[9] The location of the infarction, the duration of the QRS complex and the extent of ST elevation have direct correlation with adverse events in MI. Analyzing the ecg following treatment

can help in assessing success of reperfusion strategies. Electrocardiographic ST-segment resolution strongly predicts outcome in STEMI patients but is a better predictor of an occluded artery than of a patent infarct-related artery.[35]ST-segment resolution in combination with cardiac biomarkers (e.g., troponins, natriuretic peptides) provides powerful prognostic information early in the management of STEMI patients.[36]

SERUM MARKERS OF CARDIAC DAMAGE

With the advent of serum cardiac markers, clinicians are able to identify cases of MI which have gone undiagnosed previously.[37]

However despite its importance, care should be taken that the initiation of treatment does not depend on the cardiac marker assay. Because there is an urgency for reperfusion in STEMI, the 12-lead ECG is more than adequate to initiate treatment.

Following an ischemic attack the membranes of the myocyte become increasingly permeable, leading to a leak of intracellular molecules into the systemic circulation.[38,39] How and when these macromolecules are released into blood depend on multiple factors, including molecular weight, local blood flow, and rate of elimination.[40]

Creatine Kinase

Serum CK activity rises within 5 to 8 hours after myocardial infarction and declines to normal within 2 to 3 days . Usually the peak levels of CK occur at about 24 hours although it can occur earlier as a result of reperfusion therapies.Although serum CK concentration can accurately predict STEMI, plenty of false positives can occur with alcohol intoxication, muscle injury, pulmonary embolism and seizures. [41]Three isoenzymes of CK exist (MM, BB, and MB). Rather than depending on a single value, the rise and progression of repeated values should be observed.

CARDIAC SPECIFIC TROPONINS

Three subunits make up the troponin complex. Troponin C binds to calcium, troponin I (TnI), binds to actin and prevents actin-myosin interactions, and troponin T (TnT), binds to tropomyosin. Following myocyte death, cTnI and cTnT gets released from the cytosolic pool, followed by release from the structural (myofilament-bound) pool. One of the most important aspects in diagnosing MI is the estimation of Troponins.[42] For the Troponins, there is no fixed value above which it becomes abnormal. Rather, a recording above that of 99% of a control group is significant. [42]

Whereas when CK-MB usually increases ten times the normal value, cTnT and cTnI typically increase more than 20 times above its normal range. The

troponins can remain elevated in blood for 10 to 14 days and this can be made use of in the late diagnosis of MI. Therefore it has become imperative to measure troponins in all cases of suspected ACS

OTHER LABORATORY FINDINGS

Hematologic Findings.

The neutrophil count rises 2 to 3 hours following the episode of MI, reaches its peak level within 48 hours and becomes normal within a week. An epidemiological relationship has been discovered between high WBC count, particularly neutrophil count and adverse outcomes in ACS.[43]

High CRP levels have also been associated with a higher incidence of heart failure in STEMI and a higher grade of occlusion in the artery.[44]

IMAGING

X-RAY

Prominent pulmonary markings can be reflective of the raised LV end diastolic pressure. The amount of congestion and the degree of cardiomegaly on the chest film can be useful in predicting the patients who will be more prone for cardiac failure.

ECHOCARDIOGRAPHY

Echocardiography can be done for ACS patients in the coronary care unit or even in the emergency department before admission. [45] In patients with chest pain compatible with MI but with a nondiagnostic ECG, the finding of a distinct regional wall motion abnormality on echocardiography can be helpful diagnostically because it supports the diagnosis of myocardial ischemia. LV function estimated from echocardiograms correlates well with measurements from angiograms and is useful in establishing prognosis after MI.[45]

ESTIMATION OF INFARCT SIZE

The sum of ST-segment elevations measured from multiple precordial leads correlates with the extent of myocardial injury in patients with anterior MI.[46] Measuring a cardiac-specific troponin level several days after STEMI, even in cases of successful reperfusion, may provide a reliable estimate of infarct size, because such late troponin measurements reflect delayed release from the myofilament-bound pool in damaged myocytes.[47]

TREATMENT OF STEMI

THE 12 lead ECG has to be promptly obtained for any case presenting with symptoms suggestive of myocardial infarction. If the initial reading shows ST-segment elevation of 1 mm or more in at least two contiguous leads or a

new or presumably new left bundle branch block, the patient should be prepared immediately for a reperfusion strategy. Patients with an initial electrocardiographic reading that reveals new or presumably new ST-segment depression and/or T wave inversion, although not considered candidates for fibrinolytic therapy, should be treated as though they are suffering from NSTEMI or unstable angina (a distinction to be made subsequently after scrutiny of serial ECGs and cardiac biomarker measurements;

GENERAL TREATMENT MEASURES

Aspirin

Aspirin is effective across the entire spectrum of acute coronary syndromes and forms part of the initial management strategy for patients with suspected STEMI . An optimum dose of 162 to 325 mg should be administered acutely in the emergency department.[7]

Control of Cardiac Pain

One of the primary aims in management following the assessment of hemodynamic stability is the control of pain. Control of cardiac pain typically uses a combination of nitrates, analgesics (e.g., morphine), oxygen, and in appropriately selected patients, beta-adrenergic blocking agents. Beta blockers relieve ischemic pain, reduce the need for analgesics in many patients, and reduce infarct size and life-threatening arrhythmias. Avoiding early intravenous

beta blockade in patients presenting in Killip class II or higher is important, however, because of the risk of precipitating cardiogenic shock.[48]

Limitation of infarct size

The prognosis of MI depends on the amount of myocardium that is salvaged. Patients who succumb from cardiogenic shock generally exhibit a single massive infarct or a small to moderate-sized infarct superimposed on multiple prior infarctions.[49] Patients who survive major infarcts can develop left ventricular dysfunction and the long-term mortality rate is higher than for survivors with small infarcts, who have lesser chances of hemodynamic instability.[50]

Even though a lot of novel efforts are being attempted to limit the size of the infarct, early reperfusion remains the most useful in that aspect.

Reperfusion Therapy

GENERAL CONCEPTS.

Timely reperfusion of injured myocardium represents the most efficient way of restoring the balance between myocardial oxygen supply and demand.[51,52] The amount of myocardium salvaged depends on the time interval between the event and reperfusion.[53,54]. Even though the efficiency of reperfusion strategies wane with time, sometimes even late reperfusion of stenosed infarct arteries may restore contraction in hibernating myocardium.[55]

Fibrinolysis

Fibrinolysis recanalizes thrombotic occlusion associated with STEMI, and restoration of coronary flow reduces infarct size and improves myocardial function and survival over the short and the long term.[56, 57]

A total of nine trials have been conducted to study the efficacy of reperfusion using fibrinolytic methods. The results showed an 18% reduction in short-term mortality, and as much as a 25% reduction in mortality for the subset of 45,000 patients with ST-segment elevation or bundle branch block.

CONTRAINDICATIONS FOR FIBRINOLYSIS

Absolute Contraindications

- Any prior intracranial hemorrhage
- Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
- Known malignant intracranial neoplasm (primary or metastatic)
- Ischemic stroke within 3 mo *except* acute ischemic stroke within 3 hr
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (excluding menses)
- Significant closed head or facial trauma within 3 mo

Relative Contraindications

- History of chronic severe poorly controlled hypertension
- Severe uncontrolled hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)†
- History of prior ischemic stroke > 3 mo, dementia, or known intracranial pathology not covered in contraindications
- Traumatic or prolonged (>10 min) CPR or major surgery (<3 wk)
- Recent (within 2-4 wk) internal bleeding
- Noncompressible vascular punctures
- For streptokinase, anistreplase: Prior exposure (>5 days ago) or prior allergic reaction to these agents
- Pregnancy
- Active peptic ulcer
- Current use of anticoagulants: the higher the INR, the higher the risk of bleeding

PARAMETER	STREPTOKINASE	ALTEPLASE	RETEPLASE	TNK T-PA
Dose	1.5 MU in 30-60 min	Up to 100 mg in 90 min (based on weight)	10 U x 2 (30 min apart) each over 2 min	30-50 mg based on weight
Bolus administration	No	No	Yes	Yes
Antigenic				
Allergic reactions (hypotension most common)	Yes	No	No	No
Systemic fibrinogen depletion	Marked	Mild	Moderate	Minimal
90-min patency rates (%)	≈50	≈75	≈75	≈75†
TIMI grade 3 flow (%)	32	54	60	63

Figure COMPARISON OF DIFFERENT FIBRINOLYTIC AGENTS

Complications of Fibrinolytic Therapy.

The most frequent complications of fibrinolysis are bleeding from mucosal surfaces. Though they are usually minor bleeds, significant bleeding can sometimes occur especially for patients undergoing catheter related procedures.[58] Cerebral hemorrhage is a rare but feared complication.

Catheter-Based Reperfusion Strategies

The diseased artery can also be opened up by a catheter-based strategy. This approach has now transformed from passage of a balloon catheter over a guidewire to include potent antiplatelet therapy (intravenous glycoprotein [GP] IIb/IIIa inhibitors and P2Y12adenosine diphosphate [ADP] antagonists), coronary stents, and thrombectomy.[7] When PCI is used in lieu of fibrinolytic therapy, it is referred to as primary PCI. A PCI performed after a failed attempt

at thrombolysis is called a rescue PCI. A strategy of routine delayed angiography and PCI after successful fibrinolytic therapy may also be considered for patients who are not at high risk.[59,60]

Surgical management

STEMI patients are currently referred for coronary artery bypass grafting (CABG) for one of the following indications: patient is persistently symptomatic following fibrinolysis or PCI, high-risk coronary anatomy (e.g., left main stenosis or more than two vessel involvement) discovered at catheterization, or STEMI complicated by ventricular septal rupture or severe mitral regurgitation caused by papillary muscle dysfunction.

ANTICOAGULANT THERAPY.

Apart from its role in further progression of the clot, heparin can help prevent complications like DVT and pulmonary embolism. For every 1000 patients treated with heparin compared with aspirin alone, there are five fewer deaths ($P = 0.03$) and three fewer recurrent infarctions ($P = 0.04$), at the expense of three more major bleeds ($P = 0.001$).[61]

The usual mandate is to continue heparin for atleast 48 hours following fibrinolysis and to maintain an activated partial thromboplastin time (aPTT) target of 1.5 to 2 times that of control.[7]

Heparin may sometimes cause thrombocytopenia through immunological mechanisms but this occurs only in around 2% of patients.[62] Bleeding is the most serious complication of MI, especially intracranial hemorrhage, when fibrinolytic agents are prescribed.[63]

Low-Molecular-Weight Heparins

An alternative for unfractionated heparin is low molecular weight heparin. LMWH decreases the incidence of reinfarctions, recurrent artery stenosis and repeated episodes of angina significantly when compared to heparin.[64]. The primary outcomes of mortality in the CREATE trial were comparatively better in patients treated with LMWH.[65]

FactorXa antagonists.

The OASIS-6 trial evaluated the specific factor Xa antagonist fondaparinux (2.5 mg subcutaneously) in 12,092 patients with STEMI.[66] It showed better results compared to placebo but was similar in efficacy profile to heparin.

ANTIPLATELET THERAPY.

Following plaque rupture, platelets play an important role in formation of thrombus.[67] In patients presenting acutely with STEMI, antiplatelet therapy reduces the composite endpoint of death and recurrent infarction.The CLARITY-TIMI 28 trial showed that the addition of the P2Y12 inhibitor

clopidogrel alongside treatment with aspirin to STEMI patients younger than 75 years of age who received fibrinolytic therapy reduced the risk of clinical events (death, reinfarction, stroke) and reocclusion of a successfully reperfused infarct artery .[68] Non enteric coated aspirin should be given as a bolus dose followed by low doses as maintenance to minimize risk of bleeding. When primary PCI is the mode of reperfusion therapy, an oral loading dose of 300 to 600 mg of clopidogrel before stent implantation is an established alternative.[69]

BETA BLOCKERS.

Betablockers have benefits that are present at the time of presentation as well as those that are life long. There is a 13% reduction in all-cause mortality (7 lives saved/1000 patients treated), 22% reduction in reinfarction (5 fewer events/1000 patients treated), and 15% reduction in ventricular fibrillation or cardiac arrest (5 fewer events/1000 patients treated).

INHIBITORS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS).

RAAS inhibitors, apart from having a favourable impact on ventricular remodeling, improves hemodynamics and reduces incidence of heart failure. Studies show that chronic administration of ACE inhibitors after a STEMI reduces ischemic events, including recurrent infarction and the need for PCI/CABG.[70]

Aldosterone blockade is another pharmacologic strategy for inhibition of the RAAS.[71]

Hemodynamic Disturbances

Left Ventricular Failure

Left ventricular dysfunction is the single most important predictor of mortality following STEMI.[72,73] In patients with STEMI, systolic dysfunction alone, or both systolic and diastolic dysfunction can occur.

Cardiogenic Shock

The most severe culmination of left ventricular failure is cardiogenic shock, the incidence of which is around 5% to 8%. This low-output state is characterized by low stroke volume, high ventricular filling pressures, systemic hypotension, and evidence of vital organ hypoperfusion .

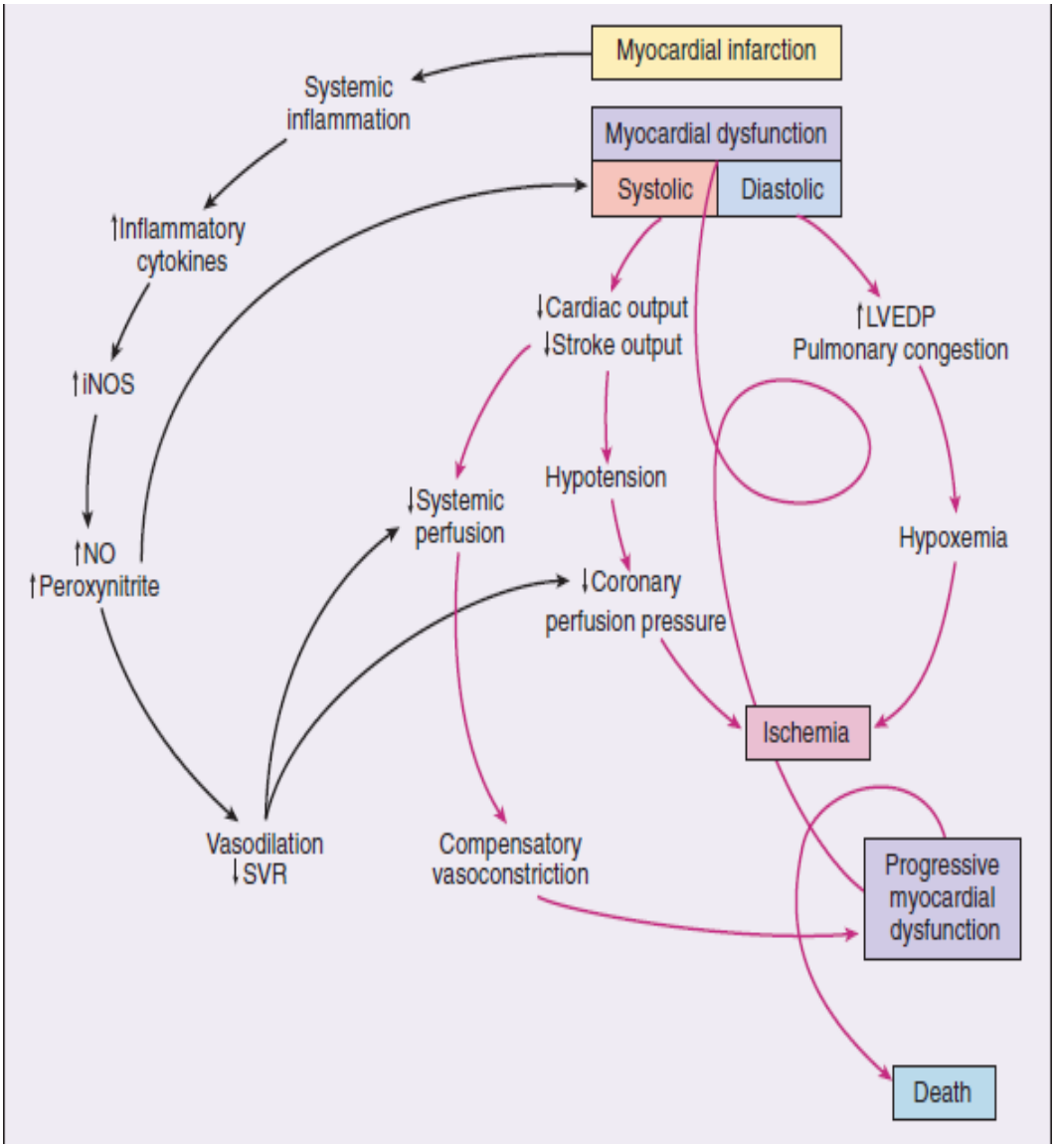


Figure-complications of acute coronary syndrome

Mechanical Causes of Heart Failure

Free wall rupture. The most dramatic complications of STEMI are those that involve tearing or rupture of acutely infarcted tissue leading to immediate hemodynamic compromise.

RUPTURE OF THE INTERVENTRICULAR SEPTUM.

Risk factors for this feared complication are increased age, presence of hypertension, anterior wall MI and late fibrinolysis.[74] Rupture of the interventricular septum almost always results in hemodynamic instability and confers a high 30-day mortality.

RUPTURE OF A PAPILLARY MUSCLE.

Papillary muscle rupture can occur as a rare but often fatal complication of transmural MI.[75,76]

ARRYTHMIAS

Arrhythmias can complicate the course of patients with ACS. They can either be bradyarrythmias or tachyarrythmias. Bradyarrythmias may be in the form of sinus bradycardia commonly seen in posterior and inferior infarctions or AV nodal blocks. Tachyarrythmias can range from benign ventricular premature depolarizations to life threatening ventricular tachycardia and ventricular fibrillation .

Dressler Syndrome

Also known as the postmyocardial infarction syndrome, Dressler syndrome presents usually with malaise, fever, pericardial discomfort, leukocytosis, an elevated sedimentation rate, and a pericardial effusion.

Left ventricular aneurysm.

True left ventricular aneurysms probably develop in less than 5% of all patients with STEMI and perhaps somewhat more frequently in patients with transmural infarction (especially anterior).[77]

MANAGEMENT OF UNSTABLE ANGINA/NSTEMI

Electrocardiography

Around 50% of patients of NSTEMI/UA present with ST depression (or transient ST elevation) and T wave changes [78]. ST segment deviation of $\geq$0.1 mV, or even 0.05 mV in the presence of a preceding normal ecg is sufficient to bring about a diagnosis of NSTEMI/UA.[78] Even transient ST elevation can occur in around 10% of cases, reflective of a higher rate of future ischemic events. T wave changes are sensitive but not specific for acute ischemia unless they are marked (>0.3 mV).

Among patients presenting with symptoms consistent with UA/NSTEMI, elevations of cardiac markers (i.e., CK-MB, Troponin T or I) identify patients with the diagnosis of NSTEMI. With the use of Troponins, which are more sensitive than CK-MB, a greater percentage of patients are classified as having NSTEMI, which is associated with a worse prognosis.[79]

Methods of Risk Stratification

High-Risk Clinical Subgroups

According to the clinical classification of unstable angina, there are certain subsets prone for increased mortality, such as secondary unstable angina, recurrent rest pain, post-MI unstable angina.[80] Also, those patients with comorbidities like diabetes, hypertension and peripheral vascular disease are at a higher risk for hemodynamic complications.[81] Similar to STEMI, patients with UA/NSTEMI who present with evidence of congestive heart failure (Killip class ≥II) also have an increased risk of death.

History
Advanced age (>70 yr)
Diabetes mellitus
Post–myocardial infarction angina
Prior peripheral vascular disease
Prior cerebrovascular disease
Clinical Presentation
Braunwald class II or III (acute or subacute rest pain)
Braunwald class B (secondary unstable angina)
Heart failure or hypotension
Multiple episodes of pain within 24 hr
Electrocardiogram
ST-segment deviation ≥0.05 mV
T wave inversion ≥0.3 mV
Left bundle branch block
Cardiac Markers
Increased troponin T or I or creatine kinase–MB
Increased C-reactive protein or white blood cell count
Increased B-type natriuretic peptide
Elevated creatinine
Elevated glucose or hemoglobin A_{1c}
Angiogram
Thrombus
Multivessel disease
Left ventricular dysfunction

FIG-CLINICAL INDICATORS OF INCREASED RISK IN UA/NSTEMI

Medical Therapy

General Measures

Patients with UA/NSTEMI at medium or high risk should be admitted to an intensive (cardiac) or intermediate care unit. The general principles of treatment are similar to that of STEMI, with obtaining adequate pain relief having prime importance.

BETA BLOCKERS.

Early placebo-controlled trials in UA/NSTEMI demonstrated the benefit of beta blockers in reducing reinfarct or recurrent ischemia.[82] In patients with acute MI (both STEMI and NSTEMI), beta blockers have also been shown to reduce reinfarction and ventricular fibrillation.

Aspirin (ASA)

Several trials have demonstrated clear beneficial effects of ASA in patients with UA/NSTEMI similar ro its role in STEMI.[83]

ADP ANTAGONISTS

Thienopyridines

These agents (ticlopidine, clopidogrel, and prasugrel) inhibit platelet aggregation by inhibiting irreversibly the binding of adenosine diphosphate (ADP) to platelet P2Y12 receptors. The addition of clopidogrel to aspirin was

studied in the CURE trial of 12,562 patients with UA/NSTEMI.[84] Clopidogrel combined with aspirin, conferred a 20% reduction in cardiac death and re infarct with aspirin alone, in all patients with UA/ NSTEMI.

Prasugrel.

This thienopyridine, like ticlopidine or clopidogrel, is a prodrug whose active metabolite is an irreversible inhibitor of the platelet P2Y12 receptor, and thereby of platelet aggregation. The TRITON-TIMI trial compared between prasugrel and clopidogrel. The primary efficacy endpoint (cardiovascular death, MI, and stroke) was reduced significantly by 19% in patients treated with prasugrel with slightly increased rates of non-fatal bleeding.[85]

Ticagrelor is a reversible blocker of the P2Y12 platelet receptor that acts directly on the platelet.[86,87] The PLATO trial showed the superiority of ticagrelor in reducing composite mortality when compared to clopidogrel.[88]

GLYCOPROTEIN IIb/IIIa INHIBITORS.

These drugs block the final common pathway of platelet aggregation, the fibrinogen-mediated cross-linkage of platelets. Abciximab, eptifibatide and tirofiban are the agents present in this class. The use of these agents have been associated with a 9% reduction in composite mortality in patients presenting with NSTEMI/UA.[89] The benefit of GP IIb/IIIa inhibition appears to be

proportionately elevated in patients presenting with a higher risk in mortality, such as diabetics and those with gross ST segment deviations.[90,91]

HEPARIN.

The use of unfractionated heparin has been a cornerstone of therapy for patients with UA/NSTEMI.[92] The addition of heparin to aspirin reduced mortality by 33% when compared to using aspirin alone.[93] Further the use of LMWH, when added to ASA, has proved to be even more effective, leading to a 66% reduction in death or MI.[93] Early trials with enoxaparin showed a 20% reduction in death, MI, or recurrent ischemia compared with UFH.[94]

FONDAPARINUX

The OASIS-5 trial compared Fondaparinux was compared with LMWH in the OASIS-5 trial in 20,078 patients with high-risk UA/NSTEMI. Its performance was non-inferior to enoxaparin for the first nine days.[65,66] However, the rates of bleeding episodes were reduced almost by half in patients treated with fondaparinux. Thus, fondaparinux is a credible alternative to heparin for patients with UA/NSTEMI.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS.

Large trials have shown a 0.5% absolute mortality benefit of early (initiated within 24 hours) angiotensin-converting enzyme (ACE) inhibitor therapy in patients with acute MI.[95]

LIPID-LOWERING THERAPY.

Long-term treatment with lipid-lowering therapy, especially with statins, has shown benefit in patients after acute MI and UA/NSTEMI .[96]

Treatment Strategies and Interventions

There are two main approaches to using invasive revascularization in UA/NSTEMI: (1) an early invasive strategy, which involves an initial catheterization followed by PCI/CABG or medical therapy based on the angiography and (2) a conservative approach, with initial medical management and catheterization at a later stage for patients who give symptoms of recurrent ischemia. To date, the efficacy of these strategies have been studied in 10 randomized trials. Of these, six trials have shown overwhelming benefit of an early invasive therapy. [97-99]

Therefore, as a result of these trials an early invasive strategy is recommended at present in patients with UA/NSTEMI who have ST-segment

changes or positive cardiac markers on admission. Hemodynamic instability and symptoms of recurrent ischemia are also indications for an early invasive strategy. An early invasive strategy is also advised in patients who present with UA/NSTEMI within 6 months of a prior PCI and in whom restenosis may be the cause. An early invasive approach is also indicated in patients with UA/NSTEMI with prior CABG.

CARDIAC BIOMARKERS AND THEIR ROLE IN THE RISK STRATIFICATION OF ACS

Markers of Myocyte Necrosis

Just as STEMI patients have high rates of mortality, patients with NSTEMI, having elevated values of biomarkers of necrosis (CK-MB or troponin), perform poorly when compared to unstable angina patients.[100] Beyond just troponin positivity, even increasing values of troponins can be helpful in gauging the severity of the episode.[101] However, in many studies, a greater risk of MI (or recurrent MI) was observed even with mild elevations of positive troponins.

C-Reactive Protein and Other Markers of Inflammation

There is an increased burden of death and MI in patients with high values of CRP at the time of presentation. Being an acute phase reactant, it is elevated by MI, with or without ST-segment elevation. So CRP is elevated five times

more in ACS patients than normal.[102] Among patients with negative Troponin I, CRP can discriminate between high- and low-risk groups. When both CRP and Troponin T are used, mortality can be stratified from 0.4% for patients with both markers negative, to 4.7% if either CRP or Troponin is positive, to 9.1% if both are positive.[103] CRP measured after stabilization post-ACS strongly predicts outcome after 3 to 12 months.[104]

	POSSIBLE MECHANISM
Markers Predicting the Development of ACS	
von Willebrand factor[1]	Mediates platelet adhesion, aggregation (at high shear stress), and stabilizes factor VIIIc
Erythrocyte membrane–bound interleukin-8[2]	Increases inflammatory response on release from erythrocyte membrane during intraplaque hemorrhage
Platelet collagen receptor glycoprotein (GP) VI[3]	Enhances platelet aggregability
Platelet-bound stromal cell–derived factor 1[4]	May play a role in vascular and myocardial remodeling or regeneration
Linoleic acid[5]	Varies inversely with low-density lipoprotein Other undefined mechanism
Trans isomer of oleic acid[6]	Unfavorable effects on lipid profile, endothelial function, and inflammatory markers
Markers Predicting Prognosis in Patients with ACS	
Thrombus precursor protein[7]	Reflects enhanced systemic activation of the coagulation system
Chromogranin A[8]	Negative inotropy, induction of apoptosis, inhibition of catecholamine secretion, vasodilation
Free plasma homocysteine[9]	Causes endothelial damage and dysfunction

Figure EMERGING MARKERS IN ACS AND THEIR UNDERLYING MECHANISMS

Study of other inflammatory markers has offered consistent evidence of an association between systemic inflammation and recurrent adverse events, including serum amyloid A, monocyte chemoattractant protein and interleukin-6.

Neopterin, a molecule related to monocyte activation, predicts long term outcomes in MI independently.[105] Elevated levels of this inflammatory biomarker (as well as of CRP) have been found to be reduced by high doses of statins. These studies, taken together, indicate that inflammation relates to patient instability and to an increased risk of recurrent cardiac events.

White Blood Cell Count

This is an even simpler, convenient but nonspecific marker of inflammation. Several studies of have shown that high leukocyte count is associated with an increased risk of mortality and re infarct.

Myeloperoxidase**.**

(MPO) is a heme protein released during degranulation of neutrophils and monocytes during the inflammatory cascade. High MPO levels positively correlate with recurrent episodes of ischemia.[106,107]

Natriuretic Peptides (BNPand NT-proBNP).

B-type natriuretic peptide (BNP) is a neurohormone that gets released from the myocytes as a result of increased wall stress. Apart from its role in

diagnosing heart failure, BNP has an emerging role in the prognostication of ACS. Studies have revealed that in NSTEMI/UA patients, higher levels of BNP correlated with increased rates of death and hemodynamic complications.[108-110]

Creatinine.

The use of creatinine or the measurement of creatinine clearance is another simple marker for predicting adverse effects in ACS.[111] The risk of impaired renal function appears to be independent of other standard risk factors.

Glucose.

In both diabetics and non diabetics, higher values of glucose or HbA1c correlated with higher rate of complications in patients presenting with MI.[112] A synergistic relationship between hyperglycemia and inflammation has also been described.[113]

Thrombus Precursor Protein

This soluble fibrin polymer is a precursor to the formation of insoluble fibrin that may be increased in patients with acute MI. A positive correlation between thrombus precursor protein levels and the rates of adverse clinical outcomes in ACS has been observed.[114]

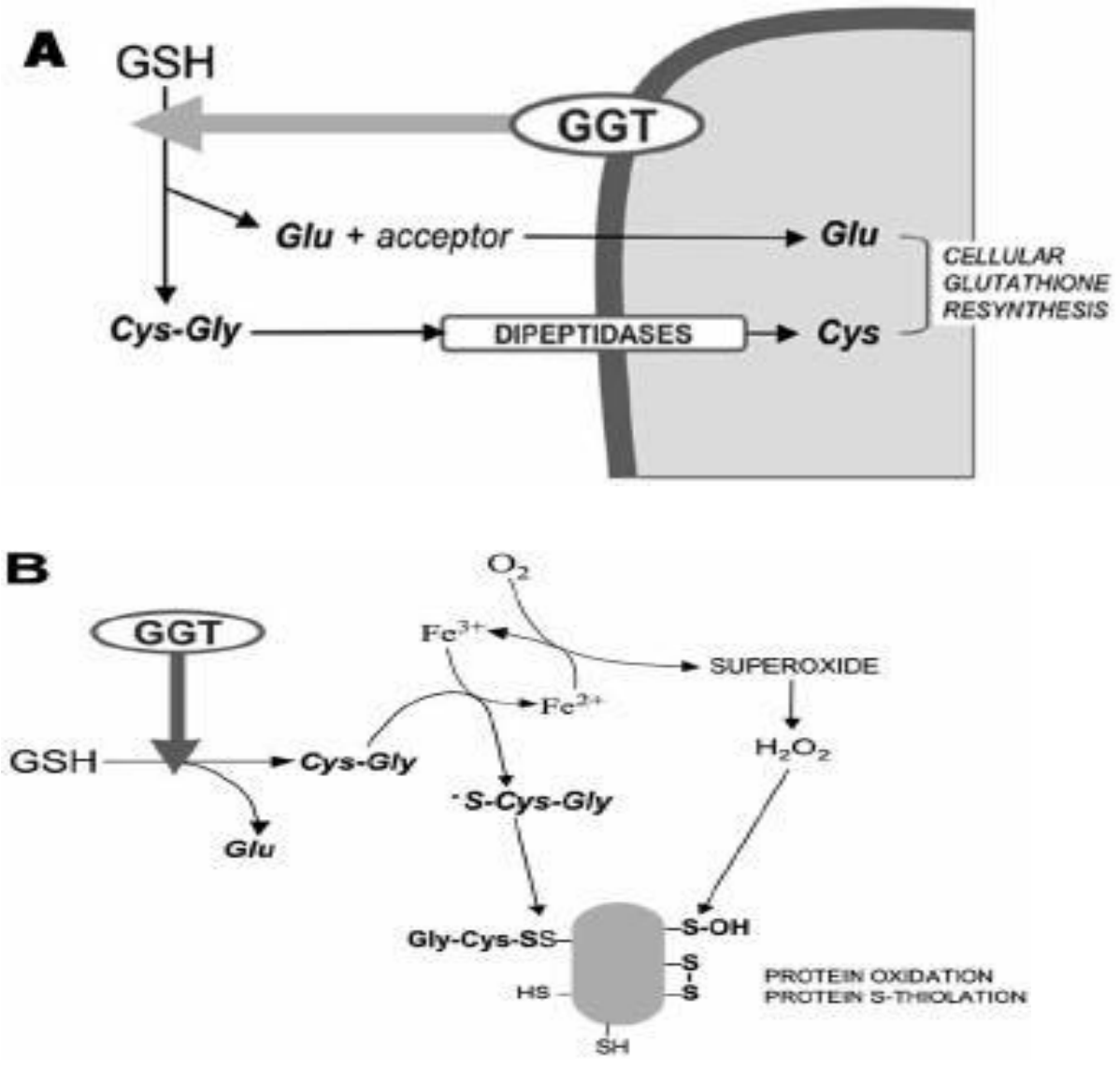
GAMMA GLUTAMYL TRANSFERASE AND ITS ROLE IN THE MANAGEMENT OF ACUTE CORONORY SYNDROME

Gamma glutamyl transferase is familiar as a serum investigation used in the diagnosis of alcoholic liver disease. However, in recent times it is being studied for its role in cardiovascular diseases with the underlying pathology of atherosclerosis. It is also being studied as a marker of severity of atherosclerotic or oxidative burden. This has practical implications in so far as it can help in selecting patients with higher risk for mortality.[115]

The basic pathophysiology behind the various manifestations of myocardial infarction is inflammation.[116] Therefore clinicians and epidemiologists have always been in the quest for ideal markers of inflammation with particular reference to ACS. However most of these markers are not commonly available or are too expensive. GGT is one of the promising enzymes being studied for its role in assessing the burden of inflammation.

Gamma-glutamyltransferase (GGT) is an enzyme involved in the constant supply of glutathione in the cell. It is involved biochemically in the breakdown of glutathione and in the process, recollects component amino acids to recycle glutathione (Fig. **1A**). Thus this cellular enzyme ensures the constant regeneration of glutathione in the cell which in turn is responsible for multiple anti oxidant reactions.[117]However, recently in a plot twist, studies are providing increasing evidence that GGT can sometimes work against the cell by

increasing the oxidative burden. This function materializes only in selected conditions, the most important of which is the proximity of transition elements like iron. This effect of GGT seems to occur when GGT is expressed in the presence of iron or other transition metals. When iron and other metals comes in concert with GGT, they get reduced ;and the electrons which get released in the process, bind to O2 molecules and make them reactive.[118] In essence, an enzyme usually involved in cellular protective reactions can sometimes cause oxidative damage to the cell.[119-121]



1). (A) GGT in its normal role in breaking down and regenerating glutathione stores.

(B) GGT causing reduction of iron followed by superoxide formation.

In other studies, GGT has been observed to be associated with raised levels of certain markers of oxidative injury. One such groups of molecules are called isoprostanes. [122,123] It has also been proven that the atheromatous lesion is rich in free iron and this can act in a permissive manner to aid the oxidant effects of GGT.[124] One of the reasons behind the progression of an atheroma has been observed to be due to oxidation of LDL molecules by superoxide ions formed as a result of GGT activity.[125-128] Hence there is increasing evidence piling up relating GGT and atherosclerotic disease processes. GGT is proving to be an important marker to efficiently stratify patients presenting with coronary artery disease as high risk or low risk.[129]

Large volume studies have also been conducted to assess the relation between traditional risk factors for atherosclerosis and GGT. These studies have shown a strong positive correlation. Some of the features significantly associated with GGT were elevated low density and total cholesterol, poor glycemic control and male sex.[130] Additionally one interesting association was between diets rich in meat and GGT. [131,132] This was possibly owing to the

higher content of heme iron in meats. Further studies are probably warranted to study permissive effects of iron and GGT in the pathogenesis of atherosclerosis.[133]

GGT-AN EMERGING MARKER IN ATHEROSCLEROTIC HEART DISEASE.

Even though GGT is traditionally being used for its role in gauging hepatic disease related to alcohol, recent studies reveal an important role in atherosclerotic heart disease.[134]

Apart from analytical studies, histological reports have also corroborated this relationship. Microscopic studies of atheromatous lesions have shown increased amount of gammaglutamyl transferase activity in its basal layers. Also, activated macrophages with increased GGT activity were found to be associated with low density lipoprotein.

Recently a subset of patients who survived acute coronary syndromes was evaluated for association between GGT and LDL in the blood. [135,136] Molecular studies revealed the close physical relationship between GGT and LDL enzyme. This is thought to be due to the peculiar biochemical organization of GGT which permits it to bind to low density lipoprotein. These studies help in incriminating GGT in its role in plaque development or rupture.

GGT AND CORONARY FLOW

The invasive revascularization strategies make use of a catheter to remove the clot in a diseased artery. However, long term studies have revealed that even after the removal of the clot, the viability of the subjacent myocardium depends on the functioning of the microcirculation.[137]Hence, even though a vessel is deemed successfully cleared by angiography, the myocardium may still suffer necrosis as a result of a dysfunctional microcirculation. [138] It has been observed that this group of patients suffers from higher rates of complications in spite of normal flow in their arteries.[139]

After much research into this phenomenon it was elucidated that these microcirculation defects are caused as a result of increased oxidative reactions at the cellular level. Keeping in mind the role played by GGT in oxidative reactions, studies were performed to correlate the GGT levels and level of perfusion in the myocardium following catheter intervention. The same studies showed a positive correlation between the two suggesting that the oxidative stress involved in disturbed microcirculation was at least partly owing to the elevated GGT load in the body.[140, 141]

Therefore patients presenting with higher levels of GGT should be anticipated for impaired myocardial salvage following invasive revascularization. Further studies will be required to assess whether a shortened

door to catheter time has a role in reducing the oxidative damage to the myocardium.

Hence, GGT seems to have the adequate characteristics of a valuable prognostic factor in MI. The prognostication achieved by this enzyme can be practically realized in the form of policy interventions such as early referral to higher centres or early revascularization. This in turn can go a long way in reducing cardiac mortality and morbidity.[142]The new role of this enzyme in oxidative reactions and atherosclerosis gives a fresh approach to our understanding of acute coronary syndrome. Further, if properly utilized, GGT can also be used in the risk scoring and treatment of MI.

AIMS AND OBJECTIVES OF THE STUDY

1. To determine the frequency of raised serum Gamma Glutamyl Transferase levels in cases presenting with acute coronary syndromes.
2. To determine the possible association between raised GGT levels and different subsets of ACS.
3. To determine the association between raised serum GGT levels and in-hospital adverse cardiovascular outcomes.
4. To determine the association between raised GGT levels and risk factors for acute coronary syndrome.

MATERIALS AND METHODS

This study was done at Government Royapettah Hospital, Chennai between May 2013 to October 2013. The study was performed after procuring informed written consent from all the participants involved. Clearance was obtained from the Ethical Committee of Government Kilpauk Medical College & Hospital Chennai.

STUDY DESIGN AND PATIENT SELECTION:

This is a cross sectional, comparative study in which seventy five cases presenting as Acute Coronary Syndrome to the coronary care unit of our hospital were selected.

INCLUSION CRITERIA

All patients admitted with an episode of Acute Coronary Syndrome in the coronary care unit of Government Royapettah Hospital.

EXCLUSION CRITERIA

1. History of any alcohol intake
2. History of hepatobiliary disease
3. Surgical conditions causing obstructive jaundice
4. Alanine transaminase (ALT)>40U/IL

5. Coarse liver echotexture on ultrasonography

6. History of taking drugs such as barbiturates, phenytoin, anti tubercular drugs

METHODOLOGY

All patients presenting with acute coronary syndrome were included in the study. Gamma glutamyl tranferase levels were measured in all the patients using a standardized photometric method with the normal value noted as **0-45 IU/L.** Blood samples were taken uniformly six hours from the time of presentation. Cases were divided into three subsets based on electrocardiographic and Troponin T measurement;

1. ST elevation MI,

2. Non ST elevation MI and

3. Unstable angina.

Patients were followed up for five days in the hospital from admission into CCU for in-hospital outcome. Major adverse cardiovascular events were recorded in the form of re-infarct, cardiogenic shock requiring inotropic support, ventricular arrythmias requiring cardioversion, pulmonary edema and cardiac death. Changes in GGT levels in ACS and its prognostic value on the development of MACE were studied.

The following investigations were done in all the patients entering into the study:

- Gamma glutamyl transferase levels
- 14 lead Electrocardiogram
- 2D echocardiography with doppler
- Total cholesterol
- LDL and HDL cholesterol
- FBS and PPBS
- Troponin T estimation
- Liver function tests
- Ultrasonography for liver echotexture

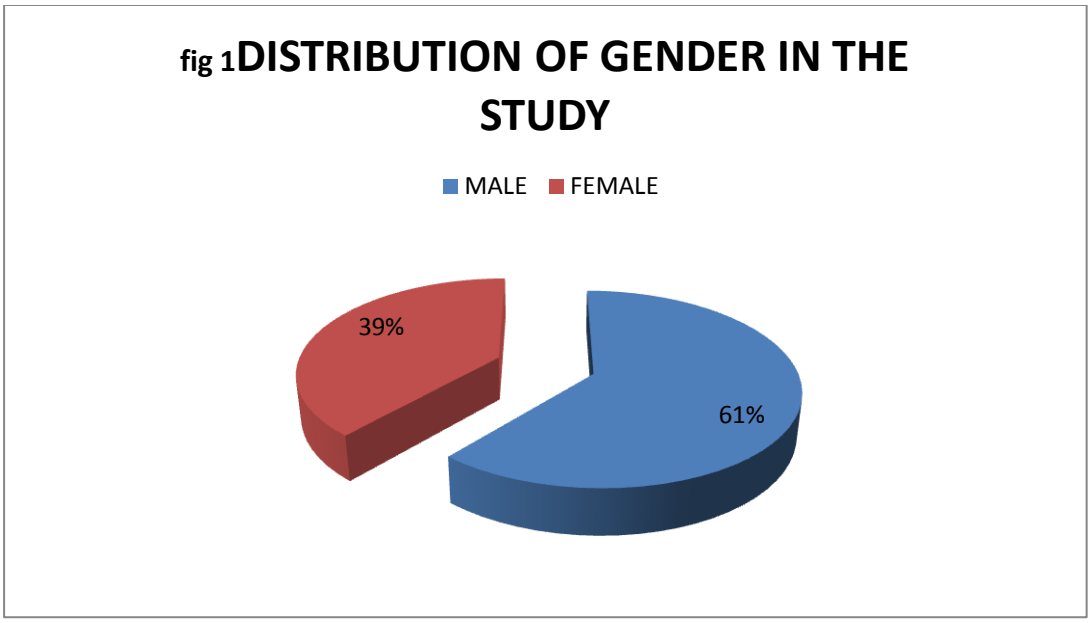
STATISTICAL ANALYSIS

Data was entered in Windows Excel format. Frequency tables and measures of central tendency (mean) and measures of dispersion (Standard Deviation) were calculated by using the statictical package SPSS- 20. Correlation was assessed using the chi-square test.

RESULTS AND OBSERVATIONS

DISTRIBUTION OF THE STUDY POPULATION ACCORDING TO GENDER AND CORRELATION WITH GGT

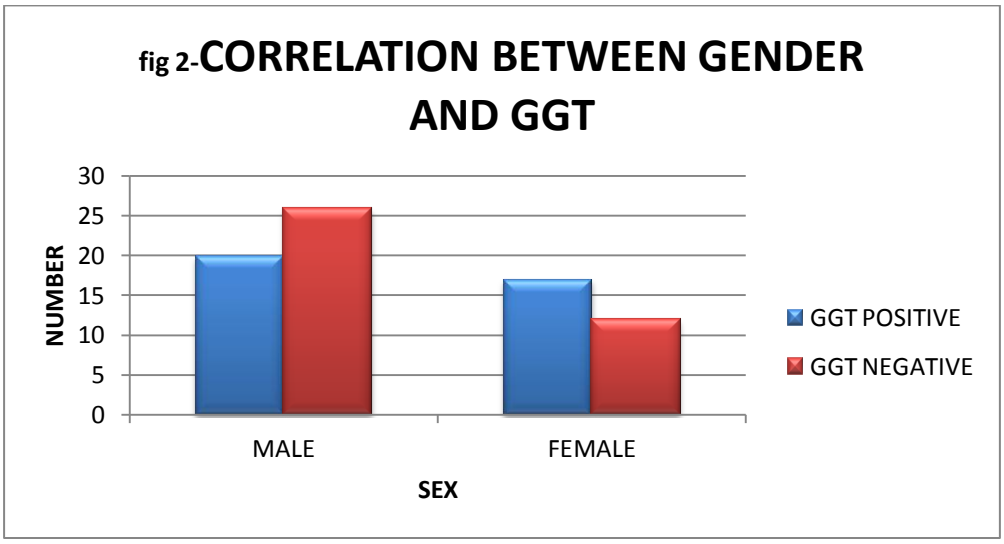
46 patients out of the study population of 75 were male and 29 were female.



Sex		GGT		Total	P value
		Positive	Negative		
Male	Count	20	26	46	
	% within Sex	43.5%	56.5%	100.0%	
Female	Count	17	12	29	
	% within Sex	58.6%	41.4%	100.0%	
Total	Count	37	38	75	**0.201**
	% within Sex	49.3%	50.7%	100.0%	
	% within GGT	100.0%	100.0%	100.0%	

Table 1- correlation between GGT and gender

20 out of 46 males had a positive value for GGT (43.5%). 17 out of 29 females were positive for GGT (54.1%).The p value was 0.201. There was no significant correlation between gender and GGT in this study.



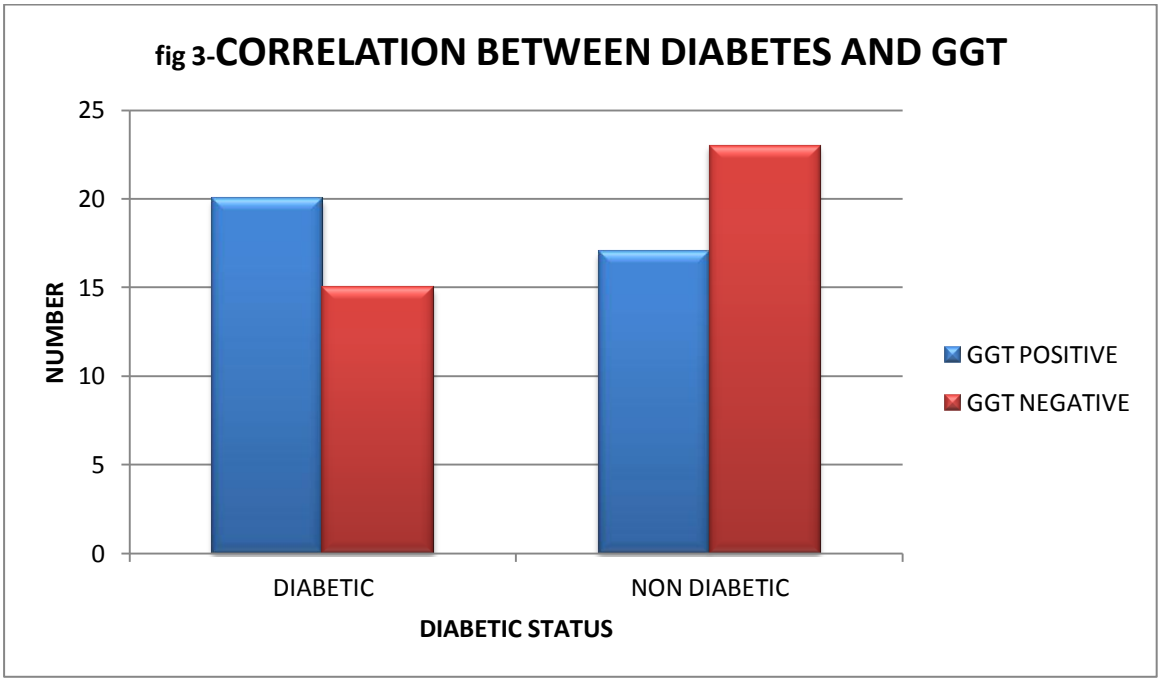
DISTRIBUTION OF THE STUDY POPULATION ACCORDING TO DIABETIC STATUS AND CORRELATION WITH GGT

			GGT		Total	P value
			Positive	Negative		
Diabetes	Yes	Count	20	15	35	0.206
		% within Diabetes	57.1%	42.9%	100.0%	
	No	Count	17	23	40	
		% within Diabetes	42.5%	57.5%	100.0%	
Total		Count	37	38	75	
		% within Diabetes	49.3%	50.7%	100.0%	

Table 2-Correlation between GGT and diabetes

35 patients out of 75 in the study population were diabetics and 40 non-diabetics. Twenty patients out of the diabetic group were positive for GGT.

Pvalue was 0.206.There is no significant correlation between diabetic status and GGT levels in this study.

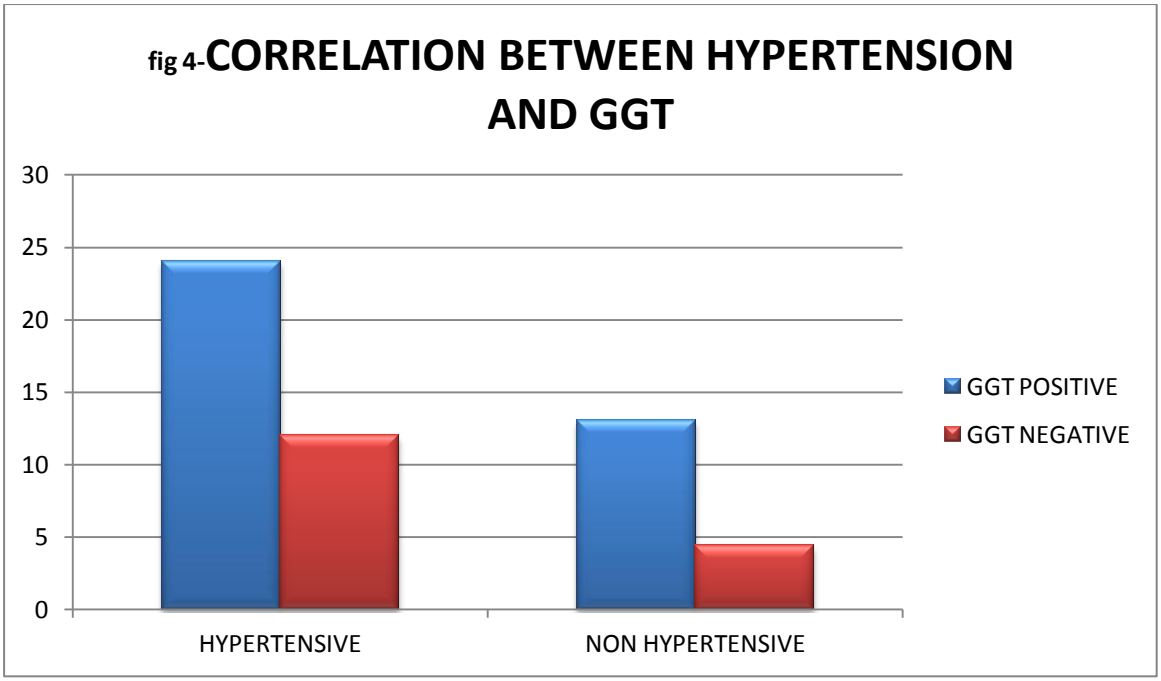


DISTRIBUTION OF THE STUDY POPULATION ACCORDING TO HYPERTENSIVE STATUS AND CORRELATION WITH GGT

Table 3- Correlation between GGT and hypertension

			GGT		Total	P value
			Positive	Negative		
SHT	Yes	Count	24	12	36	0.004
		% within SHT	66.7%	33.3%	100.0%	
	No	Count	13	26	39	
		% within SHT	33.3%	66.7%	100.0%	
Total		Count	37	38	75	
		% within SHT	49.3%	50.7%	100.0%	

Out of the 75 subjects 36 were hypertensives. 24 out of 36 hypertensives were positive for GGT. P value is 0.004. There is significant correlation between hypertension and GGT.

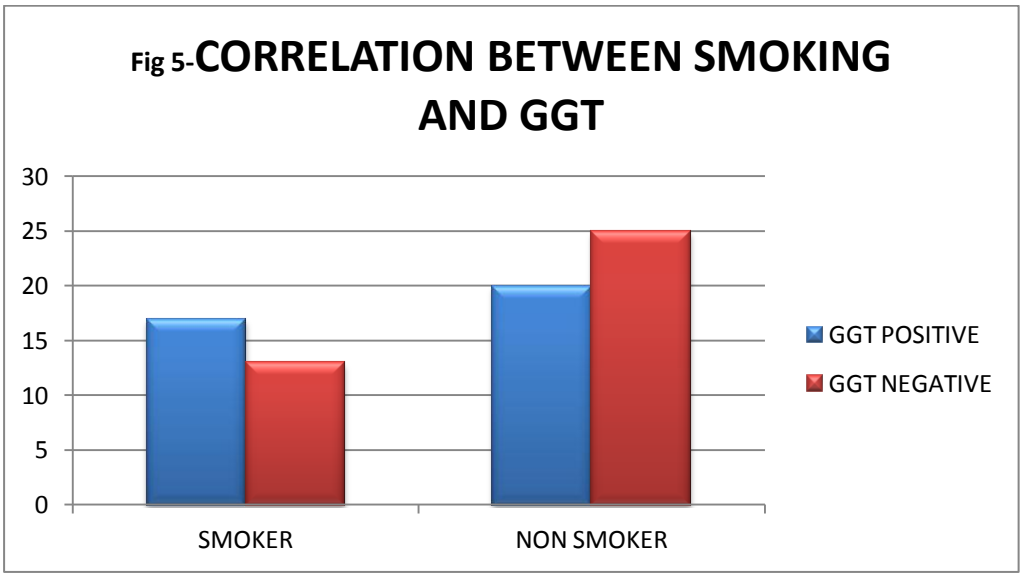


DISTRIBUTION OF STUDY SUBJECTS BASED ON SMOKING STATUS AND CORRELATION WITH GGT

Table 4- Correlation between GGT and smoking1

			GGT		Total	P value
			Positive	Negative		
Smoking	Yes	Count	17	13	30	
		% within Smoking	56.7%	43.3%	100.0%	
	No	Count	20	25	45	0.300
		% within Smoking	44.4%	55.6%	100.0%	
Total		Count	37	38	75	
		% within Smoking	49.3%	50.7%	100.0%	

30 subjects in the study population were chronic smokers. 17 of them turned out to be positive for GGT. The p value is 0.300. There is no significant correlation between smoking status and rise in GGT.

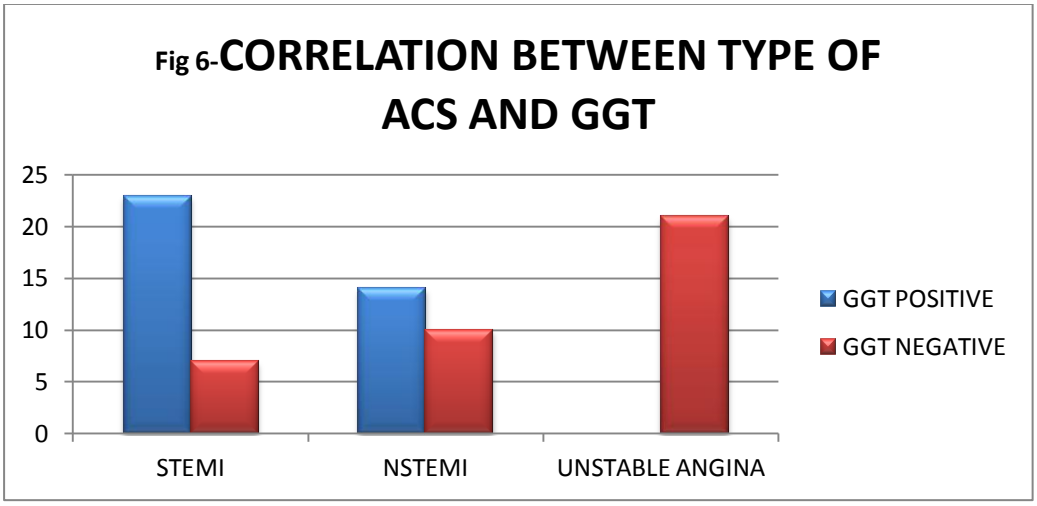


DISTRIBUTION OF STUDY SUBJECTS BASED ON TYPE OF ACUTE CORONARY SYNDROME AND CORRELATION WITH GGT VALUES

Table 5			GGT		Total	P value
			Positive	Negative		
Type of ACS	STEMI	Count	23	7	30	<0.001
		% within Type of ACS	76.7%	23.3%	100.0%	
	NSTEMI	Count	14	10	24	
		% within Type of ACS	58.3%	41.7%	100.0%	
		% within GGT	37.8%	26.3%	32.0%	
	UA	Count	0	21	21	
		% within Type of ACS	.0%	100.0%	100.0%	
Total		Count	37	38	75	
		% within ACS type	49.3%	50.7%	100.0%	

In our study of 75 patients 30 had ST elevation in their ecgs, 24 subjects suffered from NSTEMI and 21 patients had unstable angina.

23 out of 30 patients with STEMI were positive for GGT. 14 out of 24 patients were positive for GGT while none of the unstable angina subset had a positive GGT value. P value is 0.001. Therefore there is a highly significant correlation between type of ACS and GGT levels with STEMI and NSTEMI showing positive values compared to unstable angina.



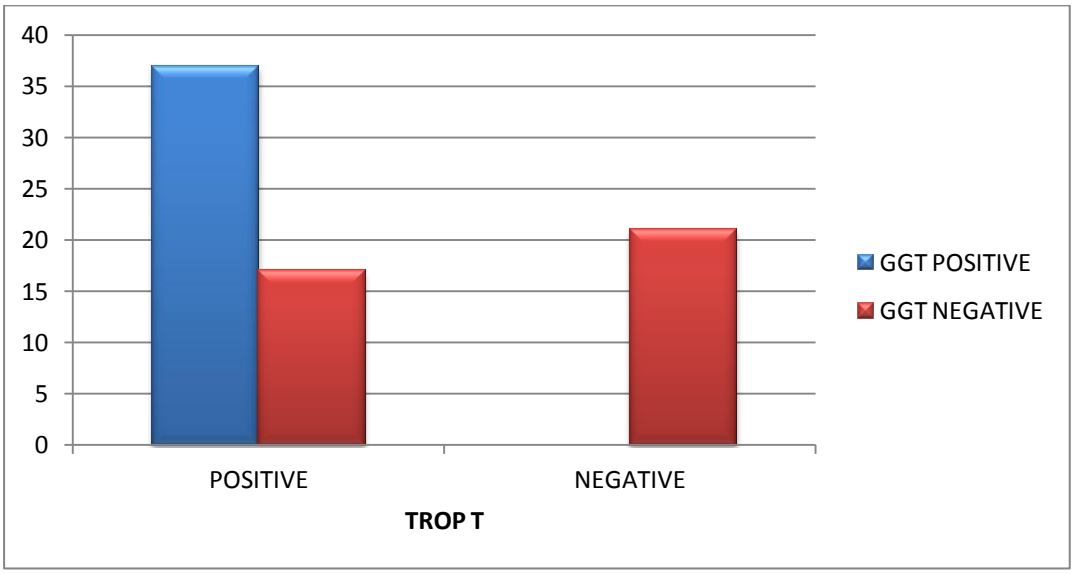
DISTRIBUTION OF SUBJECTS BASED ON TROP T POSITIVITY AND CORRELATION WITH GGT

			GGT		Total	p value
			Positive	Negative		
TROP T	Positive	Count	37	17	54	<0.001
		% within TROP T	68.5%	31.5%	100.0%	
	Negative	Count	0	21	21	
		% within TROP T	.0%	100.0%	100.0%	
Total		Count	37	38	75	
		% within TROP T	49.3%	50.7%	100.0%	

Table 6-correlation between GGT and TROP T

In the study group of 75, people with Trop T positive were 54. Out of 54 subjects, 37 of them were positive for GGT. P value is 0.001. It shows a highly significant correlation between Trop T positivity and GGT positivity.

Figure 7- Correlation between GGT and TROP T

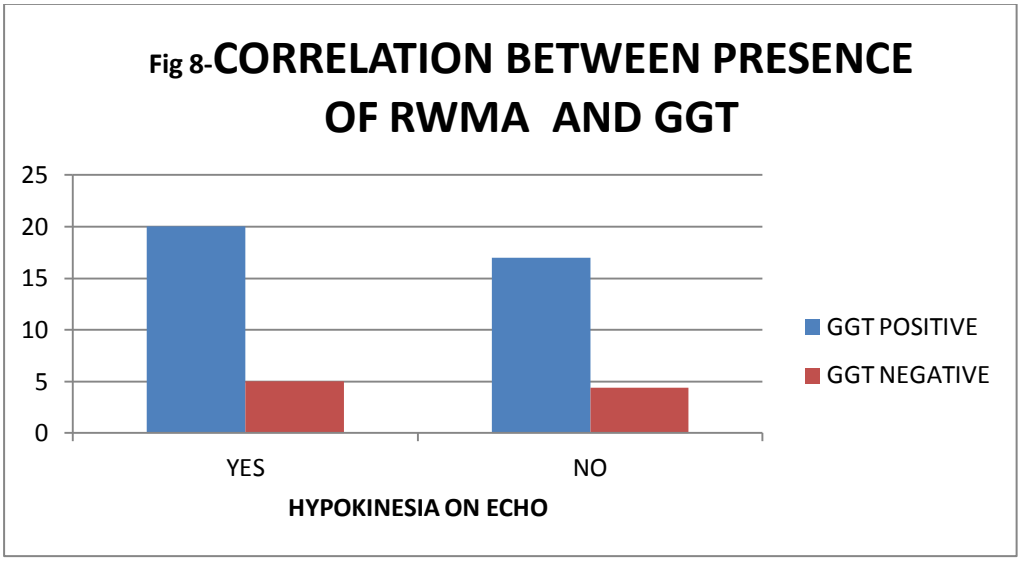


DISTRIBUTION OF STUDY SUBJECTS BASED ON PRESENCE OR ABSENCE OF RWMA (REGIONAL WALL MOTION ABNORMALITY) ON ECHOCARDIOGRAPHY AND CORRELATION WITH GGT

			GGT		Total	P VALUE
			Positive	Negative		
RWMA	Yes	Count	20	5	25	<0.001
		% within RWMA	80.0%	20.0%	100.0%	
	No	Count	17	33	50	
		% within RWMA	34.0%	66.0%	100.0%	
Total		Count	37	38	75	
		% within RWMA	49.3%	50.7%	100.0%	

Table 7-Correlation between GGT and RWMA

Out of 75 study subjects 25 had demonstrable Regional wall motion abnormality of the ventricular wall on echocardiography. Out of this subset 20 patients had positive GGT values accounting for 80%. The p value is 0.001. Therefore there is highly significant correlation between RWMA on echocardiography and GGT levels.

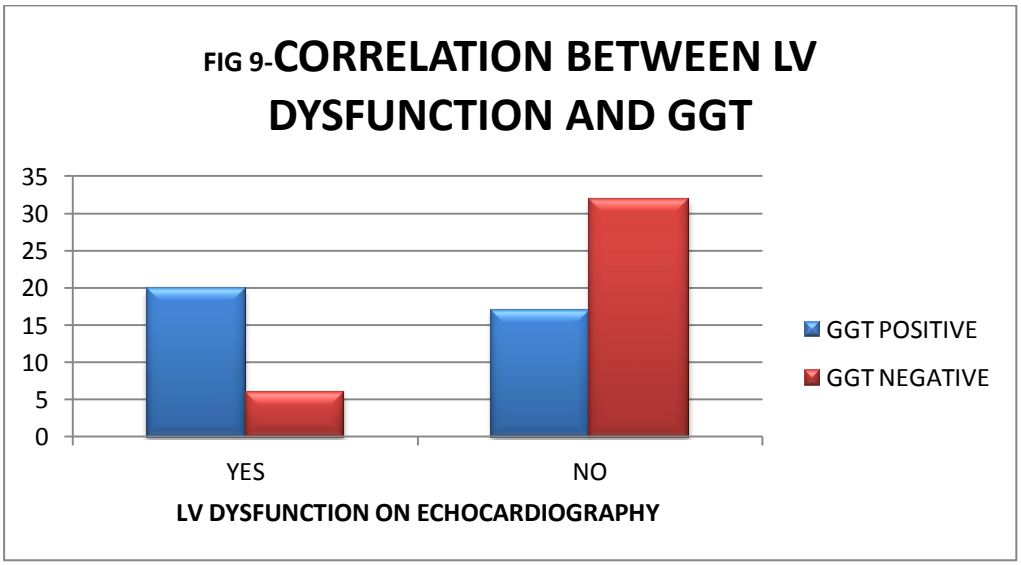


DISTRIBUTION OF STUDY SUBJECTS BASED ON PRESENCE OR ABSENCE OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION AND CORRELATION WITH GGT

			GGT		Total	P value
			Positive	Negative		
LV Dys Function	Yes	Count	20	6	26	<0.001
		% within LV Dys Function	76.9%	23.1%	100.0%	
	No	Count	17	32	49	
		% within LV Dys Function	34.7%	65.3%	100.0%	
Total		Count	37	38	75	
		% within LV Dys	49.3%	50.7%	100.0%	

Table 8- Correlation between GGT and LV dysfunction

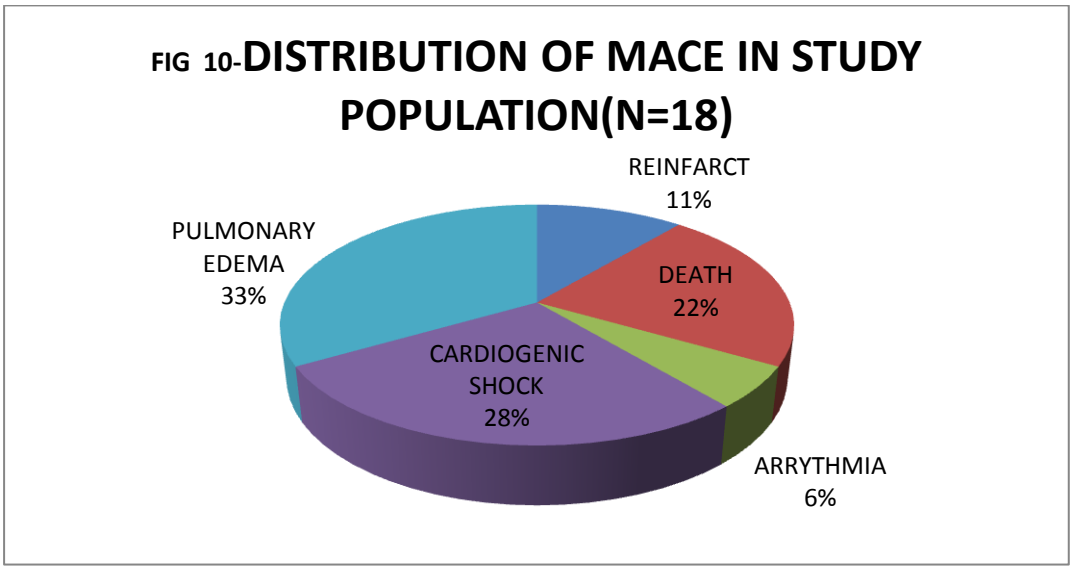
26 out 75 study subjects had systolic LV dysfunction on echocardiography as evidenced by an ejection fraction on echocardiography <50%. 20 patients out of that subset had a positive GGT value. The p value is <0.001. In this study there is a significant correlation between presence of LV dysfunction and high GGT values.



DISTRIBUTION OF STUDY SUBJECTS BASED ON EPISODES OF MAJOR ADVERSE CARDIOVASCULAR EVENTS

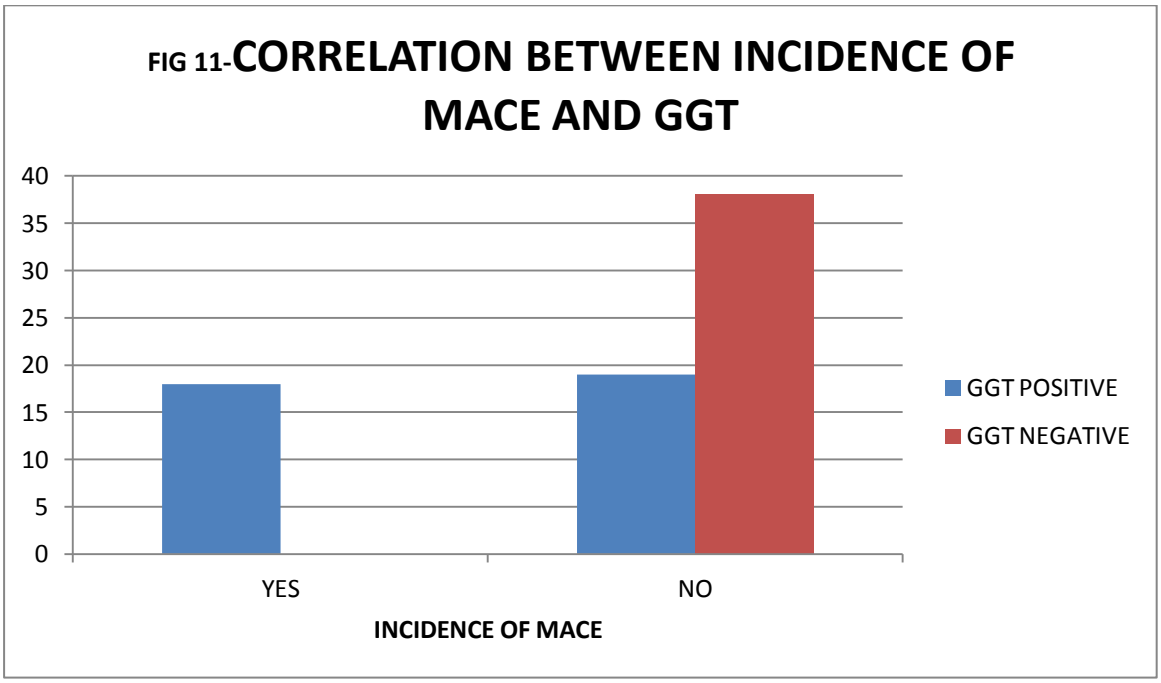
			GGT		Total	P value
			Positive	Negative		
MACE	Yes	Count	18	0	18	<0.001
		% within MACE	100.0%	.0%	100.0%	
	No	Count	19	38	57	
		% within MACE	33.3%	66.7%	100.0%	
Total		Count	37	38	75	
		% within MACE	49.3%	50.7%	100.0%	

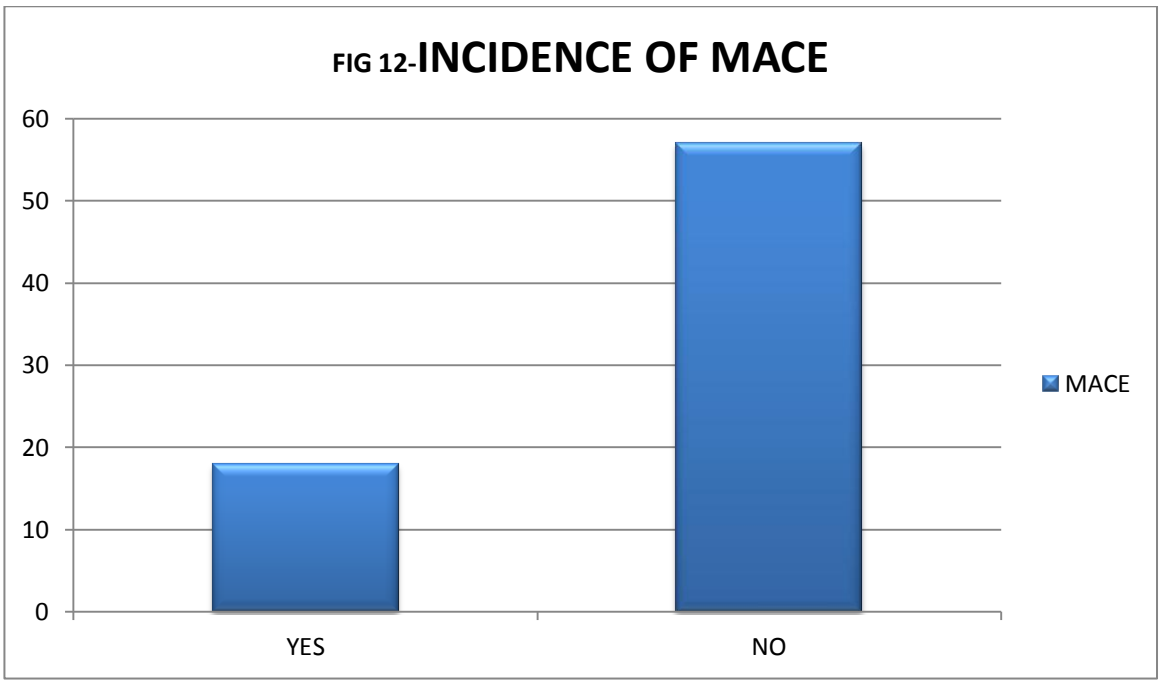
Table 9- Correlation between GGT and MACE



Out of the study population of 75, 18 subjects suffered from major adverse cardiovascular events (MACE) within their five day in-hospital period in the

form of one of the following; reinfarct, ventricular tachycardia or fibrillation requiring defibrillation, cardiogenic shock requiring inotropic support, death. All 18 patients had significantly positive GGT values. P value is <0.001. There is a significant correlation between incidence of MACE and GGT levels.

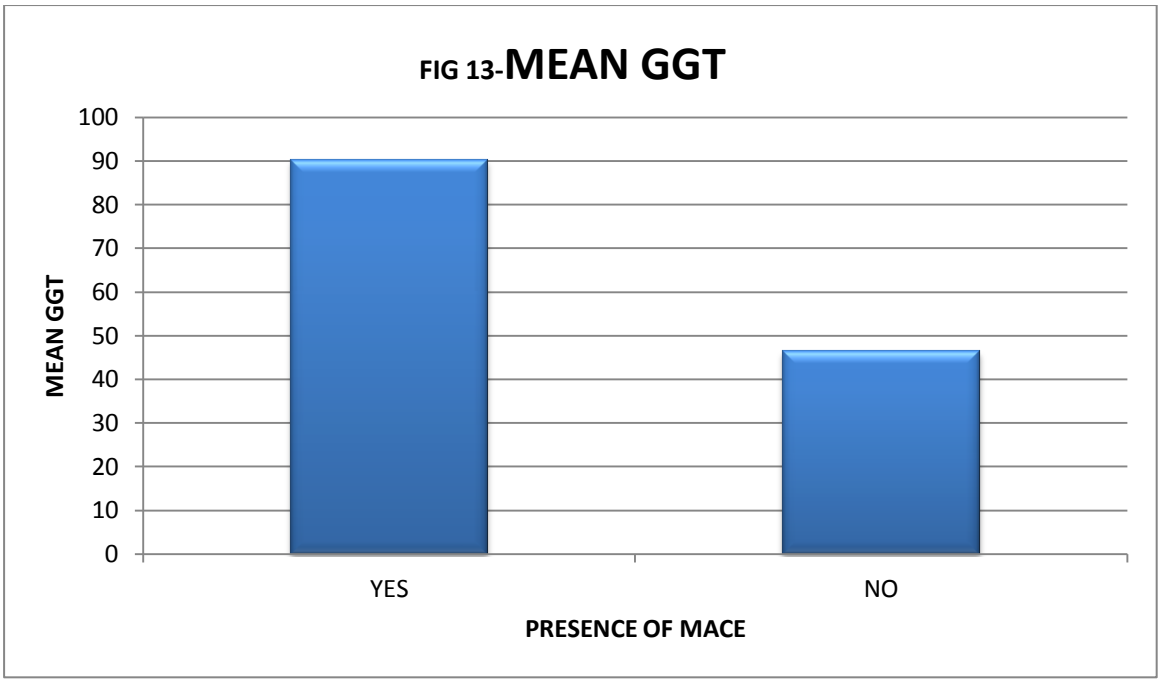




CORRELATION BETWEEN MEAN GGT AND MACE

	MACE	N	Mean	Std. Deviation	P value
GGT(IU/L)	Yes	18	90.22	7.818	**<0.001**
	No	57	46.44	19.363	

Table 10 Correlation between GGT and MACE



18 subjects suffered from one of the major cardiovascular adverse events. The mean value for these patients is 90.22. The mean GGT value for patients without MACE is a significantly less 46.44. The p value is significant with 0.001.

CORRELATIONOF OTHER VARIABLES WITH GGT

		GGT(IU/L)
Age in years	Pearson Correlation	-.030
	p value	.799
Cholesterol	Pearson Correlation	.523(**)
	p value	<0.001
LDL	Pearson Correlation	.484(**)
	p value	<0.001
HDL	Pearson Correlation	.155
	p value	0.183
BMI	Pearson Correlation	.228(*)
	p value	0.049

Table 11- Correlation of other variables with GGT

There is no significant correlation between increasing age and GGT positivity in this study. The p value is 0.799.

In comparing the total cholesterol levels with GGT, the p value is significant <0.001. therefore there is a highly significant correlation between total cholesterol and GGT.

In comparing LDL cholesterol levels and GGT, the p value is <0.001**. Therefore there is a highly significant correlation between LDL levels and GGT positivity.**

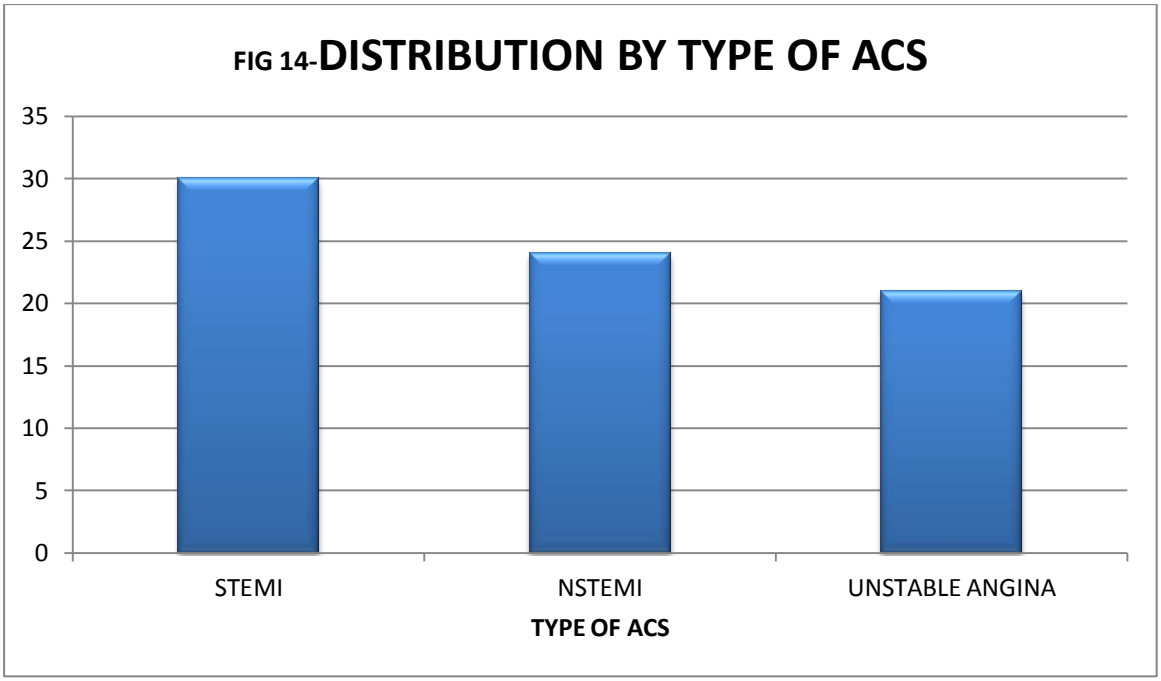
In comparing HDL levels and GGT, the p value is 0.183. Therefore there is no significant correlation between HDL levels and GGT positivity.

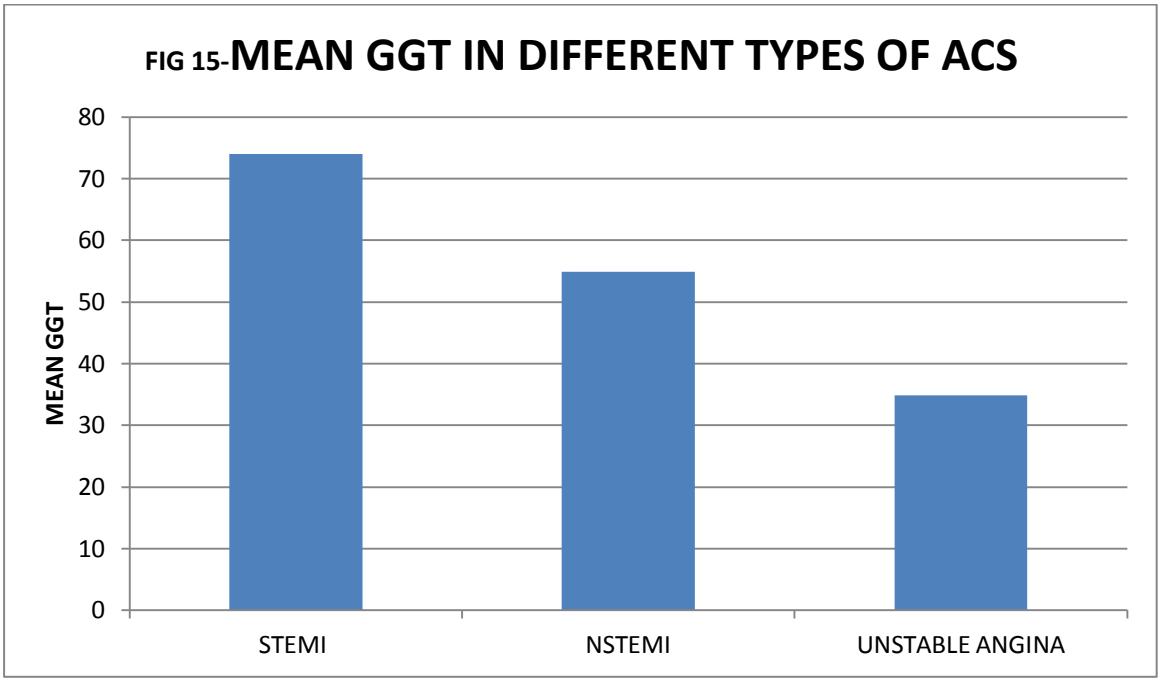
In comparing BMI of the study subjects with GGT, the p value is 0.049. **Therefore there is moderate correlation between high BMI values and GGT positivity.**

CORRELATION OF GGT VALUES IN THREE TYPES OF ACS BY ANOVA TEST

	N	Mean	Std. Deviation	P value
STEMI	30	74.03	23.348	<0.001**
NSTEMI	24	54.88	23.058	
UA	21	34.90	7.609	

Table 12- Correlation of GGT with types of ACS





ANOVA test was used to look for correlation between the three types of ACS with their respective mean GGT values. The mean GGT values for the STEMI, NSTEMI and UNSTABLE ANGINA subsets were respectively 74.03, 54.88

and 34.90 respectively. The p value was significant for this test,<0.001. Therefore the difference in GGT values in the three subsets was statistically relevant.

POST-HOC TEST

(I) Type of ACS	(J) Type of ACS	Mean Difference (I-J)	Std. Error	p value
STEMI	NSTEMI	19.16(*)	5.515	0.002
	UA	39.13(*)	5.729	<0.001
NSTEMI	STEMI	-19.16(*)	5.515	0.002
	UA	19.97(*)	6.017	0.004
UA	STEMI	-39.13(*)	5.729	<0.001
	NSTEMI	-19.97(*)	6.017	0.004

TABLE 13-GGT variation in different types of ACS

A post hoc test was calculated to compare each type of ACS with the other two types and statistically correlate the difference between them. The p value was highly significant while comparing the difference in GGT levels in STEMI with both NSTEMI and UNSTABLE ANGINA. Likewise the p value was significant while comparing NSTEMI and unstable angina with the other two subsets.

DISCUSSION

This study is a single centre cross sectional hospital based study done at Government Royapettah Hospital, Chennai. Our study population included patients admitted to the Intensive Coronary Care Unit of our hospital with Acute Coronary Syndrome during the period from May 2013 to October 2013. All the cases were divided into three subsets; ST elevation MI, non ST elevation MI and unstable angina based on electrocardiographic and TroponinT measurements. Baseline gamma glutamyl tranferase levels were measured by a standardized method for all the patients. All the subjects were observed for the first five days of their hospital stay for episodes of re-infarcts, ventricular arrythmias requiring defibrillation, cardiogenic shock requiring inotropic support, pulmonary edema and death. Multiple parameters including traditional risk factors of coronary artery disease as well as its complications were compared to GGT to look for correlation.

Age and Sex

In our study majority of patients were males (61%) and females accounted for 39% with a male: female ratio of approximately 3:2. 43.5% of males and 54.1% females had an elevated GGT value. However there was no significant correlation between gender and GGT in this study.

The age group of our patients ranged from 37 to 84 and the mean age was 60.3 with peak incidence in the fifth and sixth decades. In this study there was no statistical correlation between age and GGT.

In the study conducted by Emiroglu MY et al[129] comparing CRP and GGT, published in the North American Journal of Medical Sciences in 2010, the majority of the patients in each subset of ACS were males and male sex showed a positive correlation with GGT values. However the same study showed no correlation between age and GGT.

In the study conducted by Alexander M Strasak et al[143], the age of participants significantly modified the relation between GGT change and CVD mortality, with markedly stronger associations to be observable for younger individuals.

DIABETES

Out of the 35 diabetics in the study group 20 cases were positive for GGT. Our study showed no significant correlation between presence of diabetes mellitus and GGT positivity with a p value of 0.206.

In the study conducted by Emiroglu MY et al[129], no correlation between diabetes mellitus and GGT levels was observed.

In the study conducted by Wannamathee G et al[4] GGT values were positively correlated with diabetes mellitus.

SYSTEMIC HYPERTENSION

24 out of the 36 hypertensives in our study were positive for GGT. It showed a positive correlation between hypertensive status and GGT with a p value of 0.004.

In the study conducted by Emiroglu et al[129] there was no correlation between hypertensive status and GGT

In the study conducted by Wannamathee G *et* al[4] GGT values were positively correlated with systemic hypertension.

SMOKING AND GGT

17 out of the 30 smokers in the study group were positive for GGT. Since the p value was 0.3, there was found to be no statistically significant correlation between smoking and GGT.

In the study conducted by Emiroglu et al[129] there was no correlation between hypertensive status and GGT.

TYPE OF ACS AND GGT

In our study of 75 patients 30 had ST elevation in their ecgs, 24 subjects suffered from NSTEMI and 21 patients had unstable angina.

23 out of 30 patients with STEMI were positive for GGT. 14 out of 24 patients were positive for GGT while none of the unstable angina subset had a positive GGT value. The mean GGT value for STEMI patients was 74.03 IU/L. The mean value for NSTEMI and unstable angina were respectively 54.88IU/L and 34.90IU/L. In comparing the correlation between types of ACS and level of GGT p value was significant <0.001. The mean value in unstable angina is within normal limits. Although the mean values in the other two subsets were elevated, the *mean GGT in the STEMI subset was significantly higher than the NSTEMI subset*. This reveals that GGT shows promise as a sensitive diagnostic marker of STEMI.

The study conducted by Emiroglu et al[129] showed positive correlation between types of ACS and GGT. However there was no correlation in this study between STEMI subset and NSTEMI subset. Mean value of GGT in unstable angina subset was similar to that of control group.

In the study conducted by Dogan A et al[144] mean GGT level was higher in ACS group than control group (32 vs. 16 U/l, P=0.001).

GGT values of cases presenting with MI were higher in comparison to cases with stable angina according to the study performed by Demircan S *et al* (p<0.002)

TROP T AND GGT

Out of the 54 cases in the study that were positive for Trop T, 37 were positive for GGT. There was proven to be a significant correlation between Trop T and GGT. Further, GGT behaves similar to Trop T in that it is not elevated in any of the cases in the unstable angina subset.

In the study conducted by Emiroglu et al[129] positive correlation was seen between Trop T and GGT with a p value of 0.001.

LEFT VENTRICULAR SYSTOLIC DYSFUNCTION AND GGT

20 out of the 26 patients who were diagnosed to have systolic dysfunction on echocardiography were positive for GGT. There was a statistically significant correlation between GGT and LV dysfunction. Therefore high GGT values at presentation can assist in anticipating the complications of LV failure in patients presenting with ACS.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

A total of 18 patients suffered from MACE in the study group. Two patients suffered from re-infarct, four patients died in the hospital, five patients had to be on dopamine support for cardiogenic shock. One patient went in for hemodynamically unstable ventricular tachycardia and six cases suffered from

acute pulmonary edema. All the patients who suffered from MACE had an elevated GGT and the p value was highly significant.

The mean GGT value of the MACE subset was 90.22+7.818 and mean GGT of the non-MACE group was 46.44+19.363. Comparing the two groups too, the p value was highly significant. Hence our study shows that an elevated GGT level at presentation can anticipate adverse cardiovascular outcomes in ACS patients. GGT therefore can be an important tool in prognosticating MI patients based on risk.

In the study conducted by Dogan A et al[144] which included 237 cases, MACE-free survival was slightly poor in ACS patients with upper GGT tertile compared with those with lower GGT tertile (77 vs. 97%, P=0.06) even though p value was not significant.

GGT values were elevated more than normal in the subset of patients with significant complications, in the study performed by Ulus T et al[145]

Asma Kamal et al[146] found that GGT values were higher than normal in the 36 subjects who suffered adverse cardiovascular events and a sizeable percentage of this subset suffered cardiac death, with a p value<0.001)

OTHER PARAMETERS

Other parameters that were compared were total cholesterol levels, LDL levels, HDL levels and body mass index.

Comparing the total cholesterol levels and GGT, the p value was not significant. There is no correlation between total cholesterol and GGT in this study.

In the study conducted by Emiroglu et al[129] there was no correlation between total cholesterol and GGT.

In the study conducted by Wannamathee G *et al*[4] GGT values were positively correlated with total cholesterol.

Comparing LDL and GGT, the p value was <0.001. Therefore in our study, cases with higher LDL values were prone for GGT positivity. This is compatible with the recent studies which reveal GGT as playing an important role in LDL oxidation, which in turn is a hallmark of atherosclerotic heart disease.

In the study conducted by Emiroglu et al[129] no correlation between LDL cholesterol and GGT was observed.

In the study conducted by Wannamathee G et al[4] GGT values were positively correlated with LDL cholesterol.

HDL and BMI had no statistical relationship with GGT in our study.

In the study conducted by Emiroglu et al[129] there was no correlation between HDL cholesterol, BMI and GGT

A post hoc analysis was done to assess the strength of GGT in predicting different types of acute coronary syndromes. The p value was highly significant while comparing GGT levels of one subset with each of the other subsets. This once again proves the utility of GGT in differentiating different types of ACS.

CONCLUSIONS

- Gamma glutamyl transferase levels are significantly elevated above normal in patients presenting with acute coronary syndrome.
- GGT levels were independently correlated with STEMI and NSTEMI but had no correlation with unstable angina.
- There is a significant correlation between GGT levels and incidence of left ventricular systolic LV dysfunction
- The mean value of GGT was significantly elevated in patients who suffered from major adverse cardiovascular events. Patients with significantly elevated GGT values may, in future, be referred for early invasive revascularization procedures like PCI/CABG.
- In conclusion, as concerns ischemic heart disease, GGT assay seems to have the features of a good prognostic marker with optimal sensitivity of the diagnostic assay and it helps improve our ability to predict adverse events in CAD. Further its prognostic impact can be utilized in risk stratification and the need for urgent therapeutic intervention.

LIMITATIONS OF THE STUDY

1. The sample size of the study (75) was relatively small. A larger number would have strengthened our understanding of the correlation between the studied parameters.
2. There was no control group in the study. Even though the Unstable Angina subset acted as a control group in view of its almost normal GGT distribution, a subset containing people with non anginal chest pain would have given a clearer picture of the discriminatory power of GGT.
3. There is no way to know whether some subjects already had elevated GGT values or if the rise was linked to the ischemic event. Only further long term prospective studies will clearly elucidate this cause and effect dilemma.

THERAPEUTIC IMPLICATIONS

Acute coronary syndrome is one of the most common presentations to the medical casualty. Despite major advances in the diagnosis and management of this serious disorder, there is still much scope for improvement in reducing mortality and morbidity. Further, around 2%-3% of myocardial infarction cases are still missed in emergency departments leading to unforeseen fatalities.[1]

In the study done in our hospital, GGT was significantly elevated in patients presenting with ACS. In addition, the mean GGT values of the three different groups of ACS were significantly different from one another. In comparing the correlation between types of ACS and level of GGT p value was <0.001.

Therefore GGT may have a role in diagnosing cases of myocardial infarction especially in the presence of a non-diagnostic ECG. This will help in preventing MI cases to be missed in the ED. In addition to its diagnostic role in MI, GGT also has a discriminatory capacity to differentiate between STEMI, NSTEMI and UA. GGT can hence be an important laboratory tool alongside Troponin T and the electrocardiogram in the categorization of MI.

In our study, the mean GGT value of the subset having cardiovascular complications was 90.22+7.818 and mean GGT of the non-MACE group was 46.44+19.363. Comparing the two groups too, the p value was highly

significant. Hence our study shows that an elevated GGT level at presentation can be reflective of impending adverse effects in ACS patients. Studies worldwide have shown that high risk MI patients fare better when treated with invasive revascularization rather than conservative measures. This has wide ranging policy implications in the form of early referral to a higher centre that is equipped with PCI facilities. GGT, keeping in mind its reduced cost compared to Troponins, can therefore be an important tool in prognosticating MI patients based on risk.

I would like to suggest that a high volume multi-centre study is reasonable to further study this enzyme and its merits in the management of myocardial infarction.

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ABBREVIATIONS

ACS- acute coronary syndrome

CAD- coronary artery disease

CVD- cardiovascular disease

DALY- disability adjusted life years

ATHD- atherosclerotic heart disease

GGT- gamma glutamyl transferase

CK- creatine kinase

LVD- left ventricular dysfunction

RWMA- regional wall motion abnormality

SHT- systemic hypertension

DM- diabetes mellitus

STEMI- ST elevation myocardial infarction

NSTEMI- non ST elevation myocardial infarction

UA- unstable angina

LDL- low density lipoprotein

HDL- high density lipoprotein

TC- total cholesterol

BMI- body mass index

QUESTIONNAIRE PROFORMA

ASSOCIATION OF RAISED GAMMA GLUTAMYL TRANSFERASE LEVELS IN PATIENTS WITH ACUTE CORONARY SYNDROME AND CORRELATION WITH THEIR IN-HOSPITAL OUTCOME

NAME:

AGE:

SEX:

ADDRESS:

TELEPHONE NUMBER:

OCCUPATION:

HISTORY OF DIABETES MELLITUS AND SYSTEMIC HYPERTENSION

DRUG HISTORY:

Phenytoin

Barbiturates

Anti tubercular drugs

Carbamazepine

Anabolic steroids

Psychotropic drugs

PERSONAL HISTORY:

Alcoholism

Smoker

HISTORY: h/o of chest pain

h/o of previous IHD

h/o systemic hypertension

h/o CKD

h/o surgeries

h/o alcohol consumption /drinking pattern

h/o smoking (in pack years)

h/o jaundice, acsites

EXAMINATION

HEIGHT:

WEIGHT:

BMI:

PULSE RATE:

PERIPHERAL PULSES EXAMINATION:

BLOOD PRESSURE:

RECORDINGS	READING
SITTING	
SUPINE	

GENERAL EXAMINATION:

SYSTEM WISE EXAMINATION:

CVS:

RS:

P/A:

CNS:

INVESTIGATIONS

Complete blood count:

Hb:

ESR:

TC:

DC:

Chest Xray :

Serum Bilirubin:

ALT/AST :

ALP:

TEST	*REPORT*
1.FASTING PLASMA GLUCOSE (mg/dl)	
2.POST PRANDIAL PLASMA GLUCOSE(mg/dl)	
3.FASTING TRIGLYCERIDES (mg/dl)	
6.FASTING TOTAL CHOLESTEROL (mg/dl)	
8.LDL	
9.HDL	
10.GGT	
12.ECG	
13.ECHOCARDIOGRAPHY	
14.TROPONIN T	

MACE	NUMBER	DAY
1.CARDIOGENIC SHOCK		
2.PULMONARY EDEMA		
3.RE-INFARCT		
4.VENTRICULAR TACHY		
5.DEATH		

SL NO	NAME	AGE	SEX	DIABETES	SHT	SMOKING	TYPE OF ACS	CHOLE	LDL	HD	TROP T	GGT(IU/L)	HYPOKINESIA	LV DYSFUNCTION	BMI	GGT(+/-)	MACE
1	Ranjini	68	F	YES	YES	NO	STEMI	212	141	42	POSITIVE	94	YES	YES	25.6	POSITIVE	YES
2	Muthu	72	M	YES	NO	NO	NSTEMI	204	109	34	POSITIVE	65	NO	NO	23.8	NEGATIVE	NO
3	Rajendran	70	M	NO	YES	YES	STEMI	207	125	37	POSITIVE	42	YES	NO	24.4	NEGATIVE	NO
4	Sadiq Basha	47	M	YES	YES	YES	STEMI	219	115	42	POSITIVE	86	YES	YES	28.6	POSITIVE	NO
5	Narayanan	54	F	YES	YES	NO	NSTEMI	178	100	56	POSITIVE	71	NO	NO	27.4	POSITIVE	NO
6	Saleem	56	M	NO	NO	YES	UA	188	123	47	NEGATIVE	42	NO	NO	25.5	NEGATIVE	NO
7	Lokanathan	84	M	NO	NO	NO	UA	204	121	38	NEGATIVE	40	NO	NO	23.2	NEGATIVE	NO
8	Zaheera Bee	68	F	NO	YES	NO	NSTEMI	188	111	36	POSITIVE	32	NO	NO	25.9	NEGATIVE	NO
9	Shekar	42	M	YES	YES	NO	STEMI	190	107	50	POSITIVE	86	NO	YES	27.4	POSITIVE	NO
10	Sivakumar	65	M	YES	YES	YES	NSTEMI	244	168	64	POSITIVE	89	YES	YES	24.8	POSITIVE	YES
11	Shakuntala	38	F	NO	NO	NO	STEMI	207	96	57	POSITIVE	78	YES	YES	22.9	POSITIVE	NO
12	Krishnaveni	65	F	YES	NO	NO	UA	204	102	56	NEGATIVE	26	NO	NO	27.7	NEGATIVE	NO
13	Sakthivelu	72	M	YES	YES	NO	NSTEMI	212	116	37	POSITIVE	31	NO	NO	24.3	NEGATIVE	NO
14	Eswari	74	F	NO	NO	NO	UA	195	95	55	NEGATIVE	35	NO	NO	28.6	NEGATIVE	NO
15	Suresh	67	M	YES	YES	YES	STEMI	190	115	52	POSITIVE	77	YES	YES	26.9	POSITIVE	YES
16	Kalimullah	45	M	YES	YES	YES	NSTEMI	200	124	32	POSITIVE	28	NO	YES	22.5	NEGATIVE	NO
17	Logu	33	M	NO	YES	YES	NSTEMI	178	95	56	POSITIVE	69	NO	NO	25.5	POSITIVE	NO
18	Janaki	58	F	NO	NO	NO	UA	170	95	38	NEGATIVE	28	NO	NO	21.1	NEGATIVE	NO
19	Rajkumar	62	M	YES	NO	YES	UA	195	120	32	NEGATIVE	45	NO	NO	23.3	NEGATIVE	NO
20	Raheem	69	M	NO	YES	NO	NSTEMI	232	129	36	POSITIVE	30	NO	NO	22.8	NEGATIVE	NO
21	Inayathulla	55	M	YES	NO	YES	NSTEMI	204	115	55	POSITIVE	82	NO	YES	27.5	POSITIVE	NO
22	Maryamma	59	F	YES	NO	NO	STEMI	258	148	39	POSITIVE	99	YES	YES	23.8	POSITIVE	YES
23	Vasanthi	74	F	NO	NO	NO	STEMI	195	112	39	POSITIVE	38	NO	YES	24.1	NEGATIVE	NO
24	Murali	70	M	NO	YES	YES	STEMI	248	159	58	POSITIVE	88	NO	NO	21.6	POSITIVE	YES
25	Sathyan	68	M	NO	YES	YES	STEMI	256	166	55	POSITIVE	97	YES	NO	24.4	POSITIVE	YES

26	Bhaskar	58	M	NO	NO	NO	UA	177	121	38	NEGATIVE	40	NO	NO	26.8	NEGATIVE	NO
27	Lakshmi	59	F	YES	YES	NO	NSTEMI	210	140	42	POSITIVE	48	NO	YES	27.6	POSITIVE	NO
28	Vikram	55	M	YES	NO	YES	STEMI	288	170	54	POSITIVE	98	YES	YES	27.4	POSITIVE	YES
29	Nandakumar	64	M	NO	NO	NO	UA	232	140	58	NEGATIVE	42	NO	NO	26.5	NEGATIVE	NO
30	Kala	56	F	YES	YES	NO	STEMI	190	118	45	POSITIVE	78	YES	YES	22.2	POSITIVE	YES
31	Mohammad	75	M	YES	YES	NO	UA	208	153	65	NEGATIVE	33	NO	NO	23.2	NEGATIVE	NO
32	Jayamma	78	F	NO	NO	NO	UA	198	143	38	NEGATIVE	42	NO	NO	21.3	NEGATIVE	NO
33	Anthony	40	M	NO	YES	YES	NSTEMI	199	95	64	POSITIVE	28	NO	NO	23.7	NEGATIVE	NO
34	Manickavel	82	M	NO	YES	NO	UA	170	112	52	NEGATIVE	24	NO	NO	24.5	NEGATIVE	NO
35	Mohanamal	39	F	YES	NO	NO	STEMI	249	166	53	POSITIVE	36	YES	YES	22.9	NEGATIVE	NO
36	Jagatha	55	F	NO	YES	NO	NSTEMI	230	168	48	POSITIVE	82	NO	NO	27.4	POSITIVE	YES
37	Kumar	52	M	NO	NO	NO	UA	208	132	48	NEGATIVE	38	NO	NO	21.5	NEGATIVE	NO
38	Naseema	77	F	NO	NO	NO	UA	199	128	36	NEGATIVE	29	NO	NO	24.1	NEGATIVE	NO
39	Vijayan	65	M	YES	YES	YES	STEMI	240	152	52	POSITIVE	104	YES	YES	25.5	POSITIVE	YES
40	Mehboob	67	M	YES	NO	YES	NSTEMI	197	129	38	POSITIVE	33	NO	YES	26.8	NEGATIVE	NO
41	Arunachalam	53	M	NO	NO	YES	NSTEMI	234	164	53	POSITIVE	84	NO	NO	26.9	POSITIVE	YES
42	Lalitha	47	F	NO	YES	NO	NSTEMI	178	104	59	POSITIVE	31	NO	NO	24.1	POSITIVE	NO
43	Rajan	63	M	YES	NO	NO	NSTEMI	156	106	39	POSITIVE	38	NO	NO	21.1	NEGATIVE	NO
44	Shanthama	69	F	NO	NO	NO	STEMI	222	130	56	POSITIVE	66	NO	YES	26.8	POSITIVE	NO
45	Loganathan	55	M	NO	NO	YES	STEMI	243	152	40	POSITIVE	98	YES	NO	25.7	POSITIVE	YES
46	Raji	46	F	YES	YES	NO	NSTEMI	205	128	56	POSITIVE	30	NO	NO	24.1	NEGATIVE	NO
47	Krishnan	57	M	NO	NO	YES	UA	200	112	55	NEGATIVE	22	NO	NO	23.2	NEGATIVE	NO
48	Rohini	63	F	NO	YES	NO	NSTEMI	226	148	34	POSITIVE	41	NO	NO	29.3	POSITIVE	NO
49	Rajamuthu	71	M	NO	NO	NO	UA	167	84	52	NEGATIVE	31	NO	NO	23.1	NEGATIVE	NO
50	Govindan	68	M	YES	YES	YES	STEMI	178	117	48	POSITIVE	89	YES	YES	25.5	POSITIVE	YES

51	Kannan	64	M	YES	NO	YES	UA	175	111	46	NEGATIVE	33	NO	NO	22.5	NEGATIVE	NO
52	Zubeidar	55	M	NO	NO	YES	STEMI	195	106	36	POSITIVE	40	NO	NO	25.4	NEGATIVE	NO
53	Alamelu	48	F	NO	YES	NO	STEMI	192	98	42	POSITIVE	65	YES	YES	23.1	POSITIVE	NO
54	Marimuthu	66	M	YES	YES	NO	NSTEMI	210	140	48	POSITIVE	68	NO	NO	28	POSITIVE	NO
55	Kuppu	69	F	NO	YES	NO	STEMI	255	174	54	POSITIVE	95	NO	NO	24.4	POSITIVE	YES
56	Nasar	53	M	YES	NO	NO	UA	189	128	50	NEGATIVE	20	NO	NO	23.2	NEGATIVE	NO
57	Shruthi	57	F	NO	NO	NO	STEMI	212	152	32	POSITIVE	56	NO	NO	26.6	POSITIVE	NO
58	Kasim	78	M	NO	NO	YES	STEMI	246	172	44	POSITIVE	84	YES	NO	23.9	POSITIVE	YES
59	Maniyan	60	M	YES	YES	YES	NSTEMI	166	116	64	POSITIVE	58	NO	NO	25.9	POSITIVE	NO
60	Sarangi	72	F	NO	NO	NO	UA	179	138	44	NEGATIVE	40	NO	NO	23.6	NEGATIVE	NO
61	Veerappan	37	M	NO	YES	NO	UA	168	102	56	NEGATIVE	38	NO	NO	24.3	NEGATIVE	NO
62	Anwar	49	M	NO	NO	YES	STEMI	188	115	39	POSITIVE	43	YES	YES	26.1	NEGATIVE	NO
63	Kumari	55	F	YES	YES	NO	STEMI	244	162	55	POSITIVE	91	YES	YES	28.8	POSITIVE	YES
64	Kottaiyan	58	M	YES	YES	YES	NSTEMI	170	98	46	POSITIVE	83	NO	NO	25.6	POSITIVE	NO
65	Majeed	64	M	YES	NO	NO	STEMI	188	113	42	POSITIVE	76	YES	YES	22.1	POSITIVE	NO
66	Palanisamy	70	M	NO	NO	YES	NSTEMI	245	168	58	POSITIVE	91	YES	YES	23.8	POSITIVE	NO
67	Rajeswari	58	F	YES	YES	NO	STEMI	222	115	43	POSITIVE	26	NO	YES	27.1	NEGATIVE	NO
68	Prasad	52	M	YES	NO	YES	UA	210	111	53	NEGATIVE	43	NO	NO	31.2	NEGATIVE	NO
69	Sahayam	55	F	NO	NO	NO	STEMI	198	126	45	POSITIVE	78	YES	NO	28.3	POSITIVE	NO
70	Mari	69	F	NO	YES	NO	NSTEMI	209	111	64	POSITIVE	69	NO	NO	24.9	POSITIVE	NO
71	Andrews	41	M	YES	NO	YES	STEMI	206	120	56	POSITIVE	36	YES	NO	25.5	NEGATIVE	NO
72	Anbazhagan	56	M	NO	YES	YES	UA	199	125	55	NEGATIVE	42	NO	NO	29.6	NEGATIVE	NO
73	Waleed	62	M	YES	NO	YES	STEMI	228	161	44	POSITIVE	95	YES	YES	27.8	POSITIVE	YES
74	Shakira banu	67	F	NO	NO	NO	NSTEMI	184	116	50	POSITIVE	36	YES	NO	26.1	NEGATIVE	NO
75	Rosylyn	58	F	YES	YES	NO	STEMI	224	148	39	POSITIVE	82	YES	YES	28.5	POSITIVE	YES

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.2318/ME-1/Ethics/2012 Dt:04.04.2013
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on association of raised gamma glutamyl transferase levels in patients with acute coronary syndrome and their in hospital outcome" – For Project Work submitted by Dr.Rizwan Ahamed.Z., MD (GM), PG Student, Govt. Royapettah Hospital, Chennai.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE 21 MAY 2013 Kilpauk, Chennai-10.

29/5/13

CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai